

UNIVERSITY OF TORONTO MEDICAL JOURNAL



ANTIGENS AND ANTIBODIES

VOLUME XXXVIII

NUMBER 1

NOVEMBER 1960



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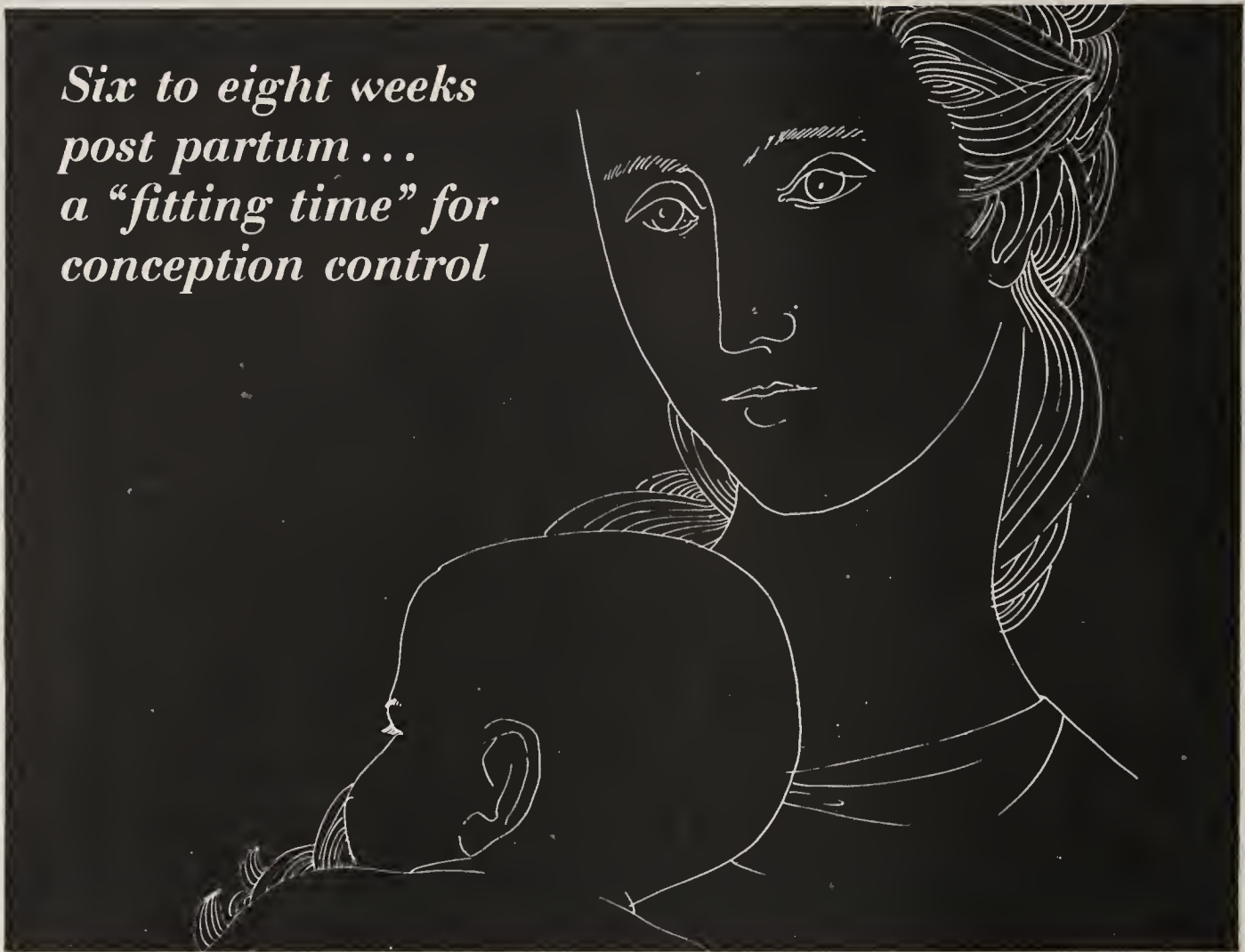
References: (1) Rebhan, A. W., & Edwards, H. E.: *Canad. M. A. J.* 82:513, 1960. (2) Editorial Comments: *Canad. M. A. J.* 82:537, 1960. (3) Brownrigg, G. M.: *Canad. M. A. J.* 73:787, 1955. (4) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M. A. J.* 77:844, 1957. (5) Royer, A., in Welch, H., & Marti-Ibañez, F.: *Antibiotics Annual 1957-1958*, New York, Medical Encyclopedia, Inc., 1958, p. 783.

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Reference: 1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.

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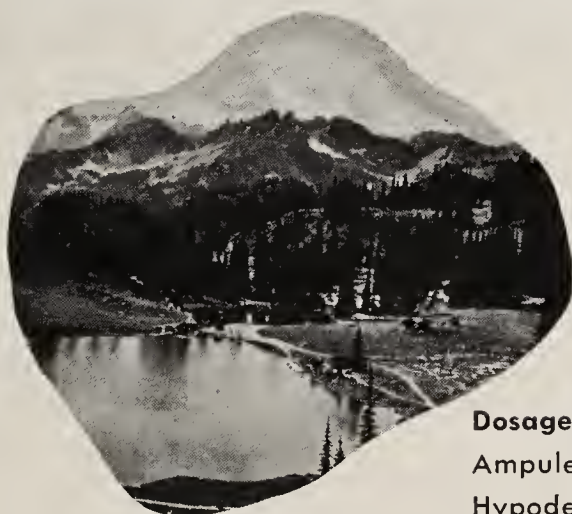
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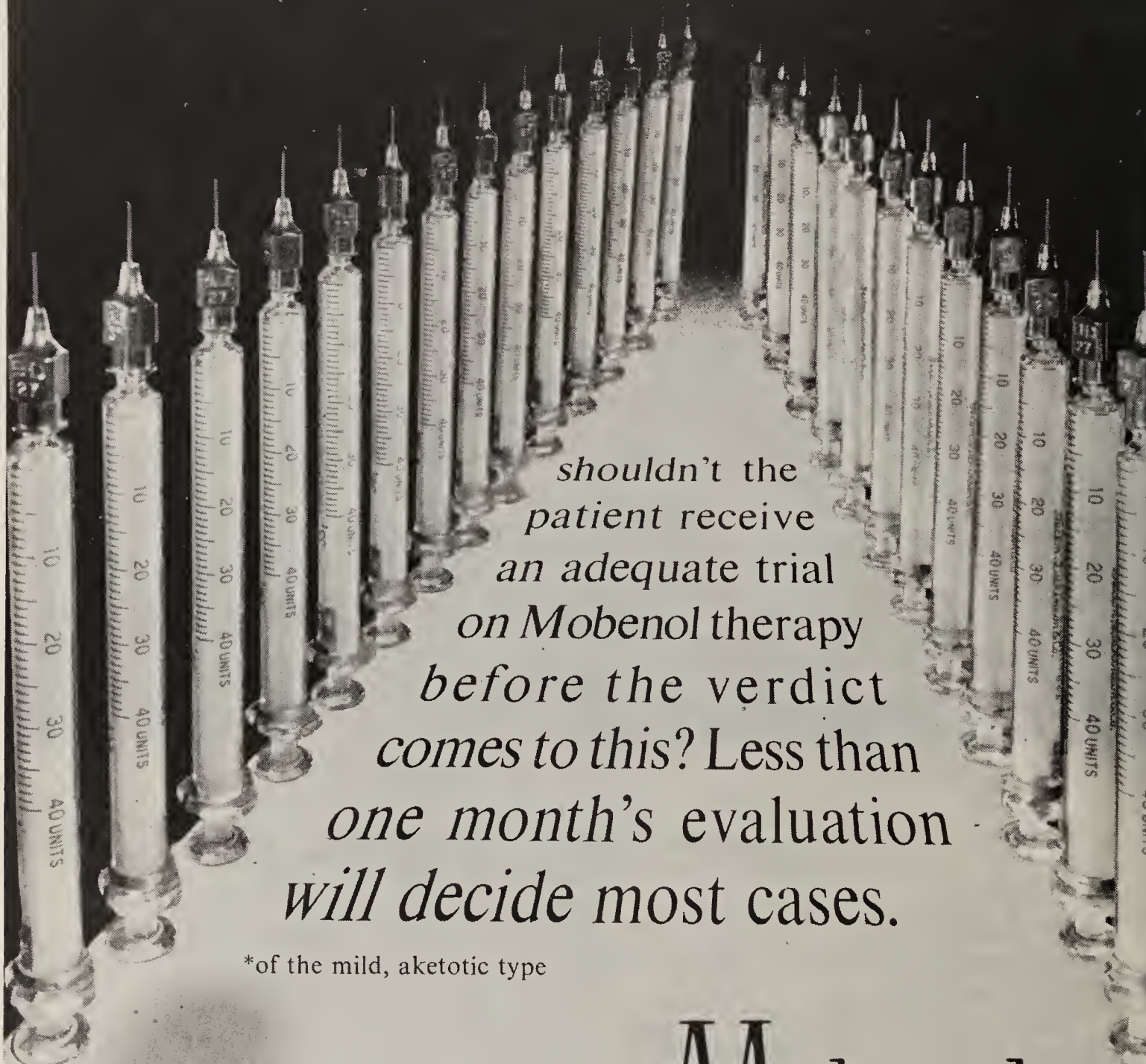
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ESTABLISHED DECEMBER 1923
AN UNDERGRADUATE PUBLICATION

NUMBER 1
VOLUME XXXVIII
NOVEMBER 1960

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This journal is published six times a year from November to April, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

Subscription rates: \$4.50 for one volume of six consecutive issues. Single copies \$.75 plus \$.10 postage.

Manuscripts including references and footnotes should be typewritten double spaced on one side of the paper. References should be kept to a minimum, and should be cited numerically in order in which they appear in the text.

Illustrations are included by arrangement with the Editor. Drawings should be done on white paper in black ink.

Final Copy Date is the 15th of the month prior to issue. Mailing date is the 15th of the month of issue.

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Authorized as Second Class Mail,
Post Office Department, Ottawa.

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EDITORIAL

TWO COMMON MYTHS

As undergraduates we are constantly being reminded that "medicine is both a science and an art". Of this we are proud, and by this we are embarrassed. The roots of this embarrassment lie in the suspicion that medicine fails to fulfill the standards of the first, and fulfills too well those of the second.

The beatification of the scientific method has embarrassed us. So impressive has been the success of the observation — hypothesis — experimentation — theory sequence, that in this new Dark Age of the penny and the popular press we are bombarded with innuendos that the virtue and validity of a science *qua* science are directly proportional to the degree it partakes of that excellence known as The Scientific Method. By these criteria, physics represents the essence of Science, and there is a fundamental difference between the kind of science pervading physics, and that predominant in the medical course. Anatomy, pathology, bacteriology and psychology are, if we believe current mythology, but pale moons dimly reflecting the rays of reason from the sun of mathematics.

Educators of the "more-science-in-our-schools" propensity have had much to say about the values of the scientific education. It is said to develop accurate observation, faithful recording, independence of thought, and truthfulness — virtues that could be proposed only by those who have never been in the undergraduate laboratory. It is said to develop clearness and logic in thought and expression; consequently, we spend no small amount of time abhorring the teleological explanation — and then go on to such scientific matters as the combination of hydrogen and oxygen to form (not *and form*) water, the storage (not *accumulation*) of glucose in the liver, and the functions (not *actions*) of the kidney.

The second myth is that art is somehow ignoble. This is intimately bound to the belief, most dazzlingly expressed by Mortimer J. Adler and the editorial columns of the Luce empire, that the only salvation for mankind from an age of man-like robots and robot-like men is a return to "the great and permanent values of the Greek and Christian tradition". Early in its history education became divided into two parts depending upon its immediate economic usefulness. This has remained, in the popular mind, at least, the main distinction between the skilled trades and the "higher learning". One of the most pernicious of Plato's concepts was that too much practical knowledge dims one's vision of "the forever true". Abetted by the tendency in our society to correlate the conspicuously wasteful and the honorific, this the greatest of the Platonic myths, still influences many in the university circle. Its influence is not limited to the humanities; indeed, it might even be suspected of playing some part in the ambivalent feelings of the university undergraduate and lecturer toward the General Practitioner. It also explains the concern of certain elements of the university for the student in the professions, that he be "well-rounded", that he be not a frail plantlet from the hot-house of specialization. Understandably, such appeals are made more often by people in "arts" to those in the professions, than vice versa; it would be a far greater sin, we are led to believe, for the medical student to graduate thinking that Pergolesi is the trade-name of a purgative, than for the artsman to graduate believing that splenectomy is the treatment of choice for the ill-tempered.

J. R. A.

EDITORIAL



ABOUT THIS ISSUE.

Volume XXXVIII, number one, marks some radical changes in the Journal as you may have gathered even now. Not only do we have a new cover, size and binding, we also have a new staff numbering thirty-three people. Since this probably the largest staff the Journal has ever had, we can hope for a little less work than formerly and you may anticipate a well-written, interesting medical magazine.

Each of the six issues this year will represent an attempt to cover a topic of prime interest and difficulty to both student and practitioner. We will not dwell on one particular specialty but aim at subjects cutting across every field of specialization. In addition to this main topic, each issue will contain other articles chosen by similar criteria. Our features will be taken from good stock and promise to delight any medical mind.

Should you wish to criticize, suggest or contribute anything, please know that we are available and interested. Subscriptions are particularly invited as they aid our financial stability and, more importantly, let us know that our words fall not only on

the deaf ears of the medical student. The cartoon shown symbolizes our position. Our thanks go to the Cambridge University Medical Society Magazine from which it was stolen, for its aptness and inclusion.

Our new cover was designed and drafted for us by my wife, Meredith, whom I wish to thank also for her help with the cover picture and some of the line drawings which appear in the text. The cut shown on the cover is a self-caricature of Oliver Wendell Holmes, (1809 - 1894) poet-physician, as a freshman medical student. The latter has since stowed his bones in grey numbered boxes but has lost none of the keenness and nattiness evident in Holmes' drawing. We thought it appropriate for the first issue.

L. E. S.

ANTIGENS AND ANTIBODIES

J. R. ALLEN, B.A., 6T1.

About 2500 B.C. Menes, ruler of Egypt, was stung by a wasp and promptly died (1). This is the first recorded allergic reaction. Two thousand years later, Hippocrates described the varied effects of cheese on mankind and gave to the western world its first description of allergy to food. Lucretius, coating his bitter pill of philosophy with the honey of poetry, sang "Quod aliis cibus est, aliis fuat acre venenum," to the Romans and thereby showed himself a keener observer than his translators. From the Dark Ages which followed him, have come tales of ladies who fainted at the presentation of a rose, and gossip of knights similarly affected by the presence of a horse.

It was not until 1901, however, that Richet and Portier gave the dog Neptune a small injection of extract from the sea anemone. A few weeks later they gave the animal a second injection no larger than the first. It became ill at once and within twenty-five minutes was dead. This phenomenon, which they called "anaphylaxis", marks the beginning of our understanding and misunderstanding of tissue damage resulting from an immunological response.

IN THE BEGINNING:

The amoeba differentiates sharply between itself and foreign substances: it engulfs them, digests them, absorbs the valuable, and expells the rest. In animals, including man, certain mesodermal cells retain this ability to recognize and reject the alien. They do so by what is called an immunological response.

When the end result of this response is protection against the foreign substance, it is said to be responsible for "immunity"; when the end result is tissue damage and physiological dysfunction, however, it is said to be responsible for "hypersensitivity". The word "allergy" was introduced by von Pirquet to describe "altered reactivity" to tuberculin injection following tuberculous infection, but subsequent use both enriched it with an aura of connotations and robbed it of exactness so that, as used today, it is roughly equivalent to hypersensitivity.

What, then, is the nature of this immunological response which brings to the animal kingdom both protection and destruction? This is the terrain which the present journal will explore — the rocky strata, the topography and finally some of the scenic wonders. In this section, we will consider substructure: the antigen, the antibody, and their union.

ANTIGENS AND ANTIGODIES: (2), (3).

To the presence of a foreign macromolecule, the body reacts by the formation of an antibody, and the macromolecule which induced this antibody response is called an antigen.

The Antigen:

The word "antigen" has two distinct meanings: it may designate a substance which reacts with an antibody or it may designate a substance which, when introduced parenterally into an animal, induces antibody formation. Most antigens fit into both categories, but there are a few important exceptions. Such an example is the Wasserman antigen — usually a soluble alcoholic extract of heart muscle and fortified with cholesterol — which reacts with antibodies in the serum of the syphilitic patient.

At present, there are no specific criteria by which we can predict the antigenicity of a substance. It may be proteinaceous or it may be polysaccharide, but there is no conclusive proof that it may be pure lipid. While the majority of antigenic substances ingested or inhaled are proteinaceous or carbohydrate, many contactants, such as plant oils, are lipid. These are generally of low molecular weight and possibly combine with molecules in the skin to form complete antigens.

In general, whatever its chemical composition, the antigen must have two properties: it must be large, and it must be alien to the circulation of the animal. In order to act as an antigen, a substance must have a molecular weight of at least 10,000. Substances of lower molecular weight are capable of combining with antibody once the antibody has been formed but, alone, they are unable to elicit the antibody response. To do this, they must be conjugated with larger molecules. Such is believed the mechanism whereby we become sensitized to simple substances — metals, drugs and dyes — and such substances are called "haptens", a word derived from the Greek *haptain*, "to bind".

Antibody production is initiated only by substances previously absent from the circulation of the animal and therefore new to antibody-forming cells; thus an antigen which will ordinarily elicit an antibody response in an adult animal will fail to do so if the animal has been injected with the same antigen before or shortly after birth — a period when antibody-forming mechanisms are not yet active. The failure of the very young animal to reject what is foreign because of its incapacity to produce antibodies

results in a changed reactivity to that particular foreign substance. This phenomenon is called "acquired immunological tolerance". (4) An example of such tolerance may be seen in cattle which have two different types of erythrocytes as a consequence of intermingling of the blood streams of non-identical twins *in utero*.

Isolated body structures such as lens tissue and thyroglobulin and body tissue modified by any means whatever — pharmacologic, degenerative, viral or bacterial — would be new to the antibody-forming cells of the body. Hence, the body might produce antibodies against its own tissue and thereby initiate an allergic reaction. Such an etiology is postulated for an ever-broadening group of diseases — the diseases of auto-sensitivity.

ANTIGENIC GROUPS AND THE MULTIVALENT MOLECULE.

The terms "antigen" or "allergen" are used to refer to a single substance such as feathers or a particular food and, more exactly, to an antigenic group present on that substance. Hence, two patients may be sensitive to the same antigenic substance but be sensitive to quite different antigenic groupings on that substance.

When an antigenic mass has more than one of the same molecular groupings it can combine with more than one molecule of the corresponding antibody; that is, the antigen is multivalent and this multivalence depends upon the number of similar molecular groups on the surface of its molecule.

THE ANTIBODIES: Those Humoral and those Cellular

There are two main groups of antibodies: in one the antibody is present and detectable in the circulating plasma and can be transferred by it; in the other, antibody is located within cells and can be transferred by leucocytes.

THOSE HUMORAL: (5).

By electrophoresis, the proteins of human serum can be separated into four main fractions — albumin and *alpha*, *beta* and the *gamma* globulin which may itself be separated into a *fast-moving gamma-1*, and a *slower-moving gamma-2*.

The *gamma* globulins are the major antibody fractions of human plasma. Electrophoretically, they form a heterogeneous group. Most anti-toxic, antiviral and antibacterial antibodies are *gamma* globulins but even a single antibody type may have a wide range of electrophoretic motility. The blocking (incomplete) Rh antibodies, for example, migrate in an agar medium as *alpha 2*, *beta*, and *gamma* globulins. At present, no clear correlations have been established

between electrophoretic properties and immunological characteristics.

The serum of some allergic individuals contains a skin-sensitizing antibody (also called reagin or reaginic antibody) which does not neutralize or precipitate the antigen (also called allergen and atopen) but is capable of passively sensitizing the skin. If the allergic patient's serum is injected into a normal person's skin, the site of injection will react with erythema, edema, and itching if subsequently injected with a small amount of the specific allergen. Studies indicate that these antibodies may be present in the *alpha*, the *beta* or the *gamma* globulin fractions. (6)

In multiple myeloma, *gamma* globulin is normal or increased in amount, but there may be no detectable increase in the antibody response to specific antigens. In short, although most plasma antibodies are *gamma* globulin, some antibodies may not be *gamma* globulins and some *gamma* globulins may not be antibodies.

GAMMA GLOBULIN:

Three types of cells have been implicated in the formation of antibodies: the lymphoid cells in germinal centres of the lymph nodes, (7), (8), and the plasma cells, (10) both those containing and those lacking Russel bodies. It may be that each of these cells responds to a different type of antigenic stimulation as was suggested by Ortega and Mellors (9). There is also some evidence, however, that the lymphocyte represents an adaptive phase and the plasma cell a productive phase in the production of antibodies.

In patients with the disease known as congenital agammaglobulinemia or, more fashionably, hypogammaglobulinemia, the lymphoid tissue resembles that of the newborn child. It shows poor corticle development of the lymph nodes, absent secondary germinal follicles and plasm cells. Like the newborn, the patient with this disease does not synthesize humoral antibodies. The child, however, does begin to synthesize *gamma* globulin between four and twelve weeks of age.

After release from the antibody-forming cells, the *gamma* globulins enter the extra-cellular fluids, where they form from 11 to 14% of the plasma protein but about 35% of the total *gamma* globulin remains interstitial. As is the case with the other plasma proteins, the individual molecules of *gamma* globulin are in a state of flux: the total amount of body *gamma* globulin being the sum total of synthesis and degradation. The catabolic half-life, that is the time required for the disappearance of 50% of the *gamma* globulin, is about twenty days. (11)

Many of the serological tests for antibodies in use today are based on reactions observed dur-

ANTIGENS AND ANTIBODIES

ing the last century. When antigen and antibody reacted in colloidal solution, a precipitate was observed. This antigen was called a precipitinogen, the antibody a precipitin. When the antigen was on a cell, the antigen-antibody reaction resulted in an agglutination. The antigen was called an agglutinin, and the antibody an agglutinin. Similarly, lysogens, bacteriolysins, that each of these antibodies is potentially capthocytes respectively to the lytic action of complement.

It is now clear that these and similar actions are but the secondary manifestations of the primary union of antigen and antibody. This primary union is not necessarily followed by such a reaction; whether it is or not depends on the nature of the antigen and its environment. Furthermore, there exists the strong possibility that each of these antibodies is potentially capable of all the various antigen-antibody reactions, but at different thresholds and with varying efficiency.

THE HUMORAL ANTIBODY RESPONSE:

Some antibodies react with antigens which, so far as can be determined, the individual has not previously encountered. These are called "natural antibodies". Some may have been elicited by sub-clinical infections, some may be present by coincidence, and some such as the isohemagglutins Anti-A and Anti-B found in human blood are genetically controlled and need not antigenic stimulation.

A single antigenic molecule may give rise to several molecules of antibody. Each molecule of diphtheria toxoid, for instance, is said to elicit the formation of about one million antitoxin molecules in a period of about three weeks. (12) A single antigenic molecule may give rise to more than one antibody type, each type having different combining properties and electrophoretic motility. Diphtheria toxoid, for example, elicits *gamma*-2 precipitating, *gamma*-2 blocking, and *gamma*-1 skin-sensitizing antibodies.

Antibodies are fairly specific. Antibodies formed in response to an antigen react with this particular antigen and usually with no other, a phenomenon referred to as "specificity". However, on occasion a weak response also occurs with some antigen other than the original one. This is known as a "cross-reaction". When an antigen is modified by heating, chemical reactions or other methods, it may lose its antigenicity or it may be capable still of eliciting antibodies, but antibodies to the modified antigens. There are, however, important exceptions, and diphtheria toxin is one: it is an antigenic poison which loses its toxicity when treated with

formalin (toxoid) but still is able to elicit antibodies which will react with the untreated toxin.

The antibody response to the injection of one antigen is sometimes impaired by the previous, simultaneous, or subsequent injection of one or more other antigens. This is known as *competition of antigens*. Conversely, the clinical use of adjuvants to obtain an enhanced antibody response in immunization is becoming increasingly popular. At present, the mechanisms of these opposing phenomena are unclear. Coons discovered that in some cases, at least, the individual plasma cells are capable of forming only one kind of antibody. Possibly the adjuvants work by increasing adsorption time and hence prolonging antibody stimulation but it is also possible that some of them, at least, may modify the cellular response. With the addition of killed mycobacteria, for example, non-living substances such as albumin may induce the delayed type of sensitization.

The antibody response seems to have a memory — for when an antigen is injected the second time, the antibody response is both more rapid and more exuberant. This is of practical value, in the case of booster doses.

If, as has been postulated, antibody formation is possible only in response to such antigenic groupings as were absent from the circulation before or just after birth — then the possible groups antigenic for any particular individual must necessarily differ from those on any of that individual's body cells; hence, both the quantity and quality of antibody response to any antigen is at least partially under genetic control.

THOSE CELLULAR:

Skin-sensitization to bacteria may be transferred to non-sensitized humans by a suspension of leucocytes from the peripheral blood of sensitized donors. (14) It may also be transferred in leucocyte extracts. Whether such an extract contains antibody or some substance more intimately concerned in cellular metabolism is unknown. By the injection of lymph nodes or spleen, (15) sensitivity may also be transferred from sensitized to non-sensitized animal.

Patients with agammaglobulinemia have little or no circulating gamma globulin. They are prone to bacterial infections but may develop normal immunity to Gram-negative endotoxins such as that of *Shigella* and to viral infections. Such experimental and clinical evidence has led to the concept of cellular antibodies. Just as the humoral antibodies are associated with immediate allergic reactions such as anaphylaxis, so the cellular antibodies are associated with delayed hypersensitivity, the classical example of

which is the tuberculin reaction. For many years such delayed reactions were thought to be induced only by living organisms, consequently it was called "bacterial allergy". Recently such delayed hypersensitivity reactions have been produced by non-living substances such as albumin when the lipoidal fraction of bacteria is added. The exact effect of such an adjuvant is unknown: it may change the antigen or it may change the cellular response.

THE MECHANISMS OF ANTIBODY FORMATION:

Present knowledge of antibody formation within the cell leaves many questions unanswered. Currently, there are three main theories: the natural selection theory of Jerne (16), the adaptive-enzyme theory of Burnett, and the modified template theory of Pauling.

A number of workers (17) independently suggested that antibodies are new globulins having surface chemical configurations such as to complement those of that juxtaposed antigen whose presence induced their formation. Pauling proposed that only the folding of the peptide chains forming the antibody was under the influence of the adjacent antigen. A very different concept was presented by Burnett who proposed that certain enzymes which destroy antigenic substances are so modified in consequence of this action that they can later synthesize antibody in the absence of antigen.

In considering antibody formation, the question of the relationship between cellular and humoral antibodies arises. Pappenheimer answers this by postulating that cellular and humoral antibodies represent successive steps in antibody formation. The primary antigen-induced antibody is located, he believes, near or on the surface of the sensitized cell. This is responsible for the phenomenon of delayed allergy and can be achieved even by patients with agammaglobulinemia. Further antigen stimulation results, according to his theory, in the capture of antigen by the pre-plasma cells which now differentiate into plasma cells and produce gamma globulin. This does not occur in agammaglobulinemia; apparently, therefore, delayed and immediate hypersensitivity are under separate genetic control.

And so, we can see that those who seek the principles of antibody formation must follow a route which soon leads from the highways of present knowledge into the magical darkness of the forest of protein synthesis — a route which is crossed by foot-paths to nucleic acid synthesis, inductive enzyme formation and genetics and but dimly lighted by the fitful moon of experiment.

ANTIGEN-ANTIBODY REACTIONS:

Since the beginning of the present century, much theoretical and experimental ingenuity has been marshalled to the defense of the opposing theories of Ehrlich who favoured chemical reaction between antigen and antibody and of Bordet who favoured the adsorption of the antigen by the antibody. The conflict is not yet resolved but at present the supporters of the chemical reaction theory hold the upper hand.

It has been pointed out above that the antigen-antibody reaction may be divided into two phases: an initial one during which the antigen and antibody combine (in multiple proportions), but there is no visible change in the media and which may or may not be followed by a second, more prolonged phase marked by specific visible phenomena such as agglutination, precipitation, and lysis.

There is considerable uncertainty whether the union of antigen and antibody in the living animal takes place in or on the cell or in the blood stream. Independently, in 1909, Friedemann and Friedberger discovered that the incubation of antigen-antibody precipitates with normal serum resulted in the elaboration of a toxic substance. Bordet demonstrated that a similar substance could be induced by the incubation of normal serum with agar or starch. It was called *anaphylatoxin*.

In the next decade, Dale and Schultz showed that washed strips of smooth muscle from a sensitized animal still contracted when specific antigen was added to the perfusion fluid. Dale (18) proposed that the contact of antigen with sensitized tissue causes the release of histamine or histamine-like substances and with the advent of this histamine-cellular theory, the concept of anaphylatoxins, whether produced by the action of proteases and other humoral factors, or not, fell into neglect for the next twenty years.

Then, in 1940, Rocha e Silva (19) demonstrated that anaphylatoxin released histamine in the Guinea pig, and this demonstration of a possible dual mechanism in allergic responses has revived interest in anaphylatoxins, proteases, and other humoral factors. The plasminogen-plasmin system in particular has been extensively investigated. (20) However, at present, the exact significance of humoral mechanisms is uncertain.

It has been known for several years that one humoral factor, complement, is vital in hemolysis and certain other antigen-antibody reactions. Becker has shown that the first of the four components of complement is an enzyme, pro-esterase. That hemolysis may occur, the cells

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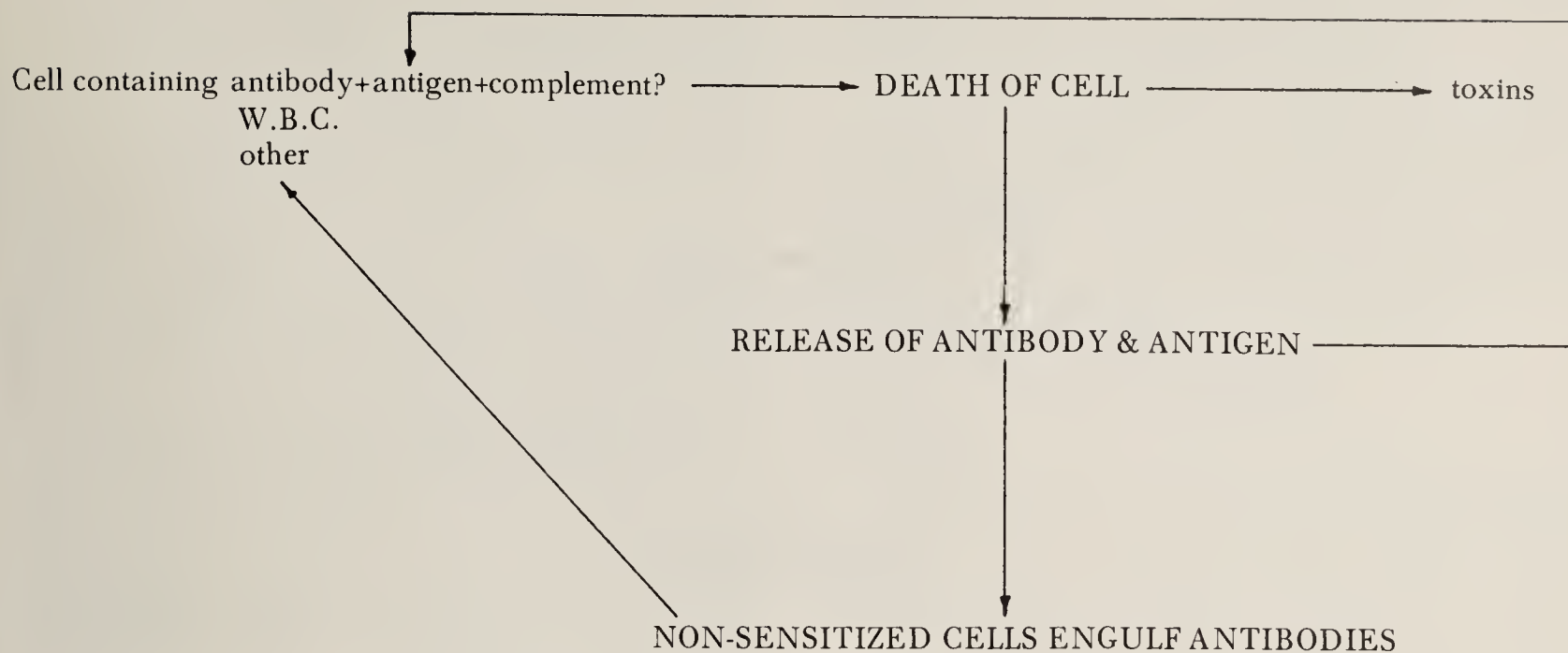


FIG. 1. DELAYED HYPERSENSITIVE REACTION Possible Mechanism As Suggested By Pappenheimer

must be sensitized. It is the sensitized cell that converts this pro-enzyme into an active enzyme thereby setting in motion a train of reactions leading eventually to hemolysis. Mongar and Schild have presented some evidence that a cellular pro-enzyme is quickly inactivated under normal circumstances, when it becomes active, but that the same enzyme will remain active when it is united with antibody, and that this active enzyme brings about the release of histamine. Hence, we have suggestive but not conclusive proof that the link between antigen-antibody union and the release of mediating substances is a single enzyme or a series of enzymes activated by the antigen-antibody union. Other investigators have put forth a replacement theory according to which histamine is replaced in mast-cell granules by some releasing substance. Which of these mechanisms, if either, is correct remains to be demonstrated.

THE MEDIATORS:

In considering mediating substances, that is, substances resulting from the antigen-antibody union and themselves affecting the body tissues — we should bear in mind two important facts. The theories resulting from experiments with animals in which sensitivity has been artificially induced are not necessarily directly applicable to spontaneous hypersensitivity such as is found in asthma and hay-fever or to the delayed hypersensitivity typified by the tuberculin reaction. There is also considerable species variation: in the mouse, for instance, the antihistamines Bena-

dryl and Pyribenzamine actually increase sensitivity to histamine.

Many of the physiological disturbances which are observed in the immediate type of allergy resemble the actions of histamine and can be inhibited by the antihistaminic drugs. (23) In some cases, as when ragweed antigen is added to a test tube of blood from a patient with hay-fever, histamine release can be demonstrated. Histamine is released when specific antigen is added to human tissue removed from allergic individuals. Histamine liberators can reproduce allergic symptoms in allergic people, and clinical improvement of symptoms parallels the development of refractoriness to these drugs. (24) Histaminase, however, does not protect from anaphylactic shock.

At present, there is evidence that many other substances in addition to histamine may be released by the antigen-antibody reaction — heparin, serotonin, acetylcholine and slow reacting substances. Possibly the importance of any one of these substances varies greatly from species to species. Possibly some of them act by releasing or inhibiting some other substance.

The histamine - release theory was criticized because it did not explain the increased coagulability of the blood that is found in anaphylactic shock. In 1941, Scroggie and Jaques (25) demonstrated the simultaneous release of histamine and heparin from the liver of the dog.

Serotonin, or 5-hydroxytryptophane, is normally present in the platelets, brain, lung, spleen and gastro-intestinal tract. In the mouse, (26) antihistaminic drugs give little protection against anaphylaxis, while lysergic acid, a serotonin an-

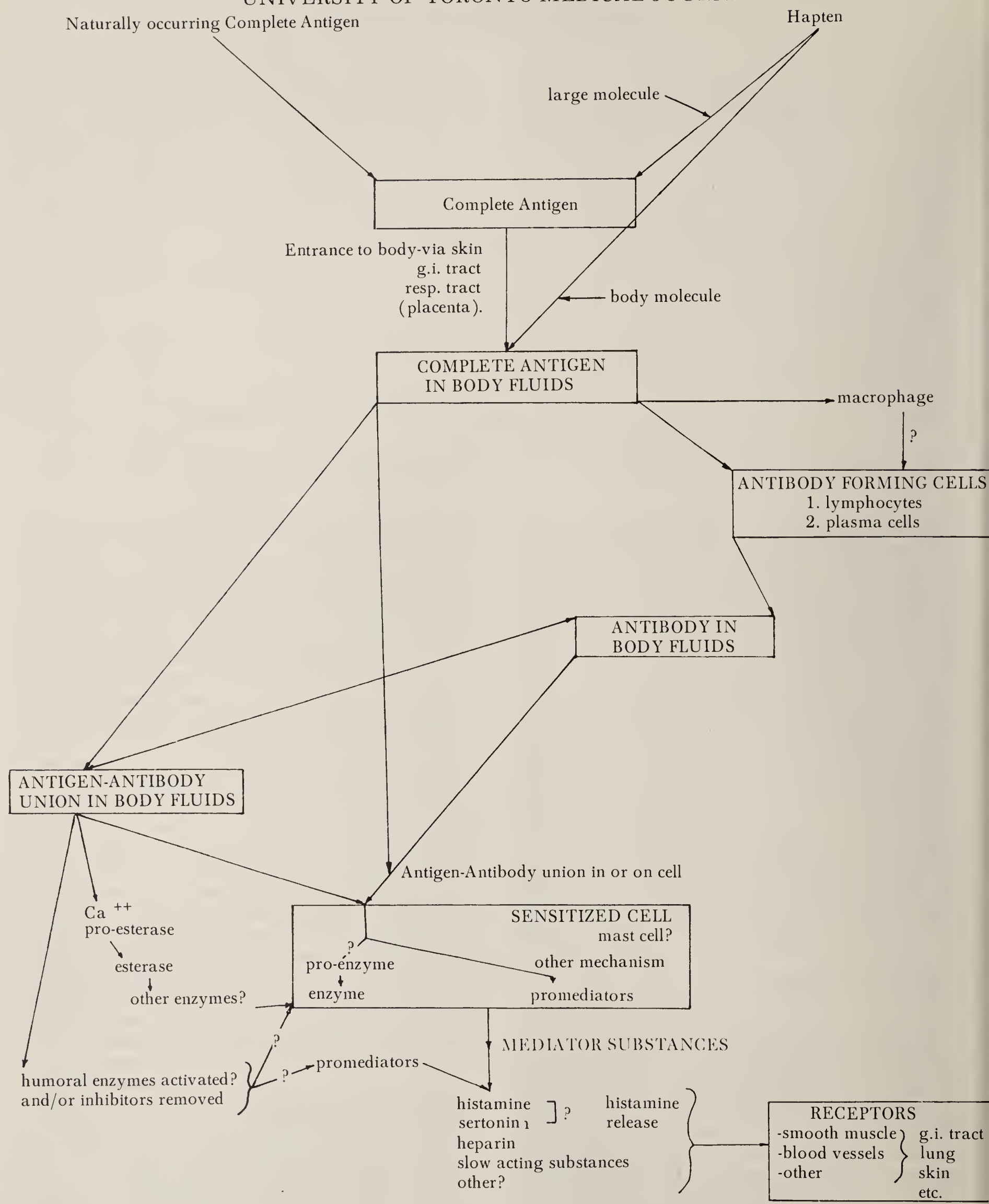


FIG. 2 POSSIBLE MECHANISM OF ACUTE ALLERGIC REACTION

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tagonist, does. In humans, the major known role of serotonin in an allergy-like condition occurs in a rare type of asthma associated with intestinal carcinoid; however, it has been reported that it does not cause spasm of the bronchial muscles on direct contact. There is some evidence that it may act as a histamine liberator.

The importance of acetylcholine in allergy is uncertain. Asthmatic attacks may be induced in patients suffering from asthma by an injection of either histamine or acetylcholine (Mecholyl). Peters and Silverman (28) demonstrated that both histamine and acetylcholine were necessary to cause urticaria on one of their patients.

The chemical structures of the slow reacting substances have not yet been determined. (29) Consequently, they are known primarily by their pharmacological properties. One of these substances is SRS-A, a lipid acid described by Kellaway and Kethewie (30) which causes bronchial contraction, is important in anaphylaxis in humans and Guinea pigs and is not affected by the presence of antihistaminic drugs.

None of the aforementioned mediators has been irrefutably implicated in producing the delayed-type of hypersensitive reaction which is typified by the tuberculin reaction. The concentration of histamine in the skin of patients with contact dermatitis is increased and is present mainly in the mast-cells and eosinophils. However, the presence of these cells may well be the result rather than the cause of the delayed reaction. (31)

ALLERGY RECONSIDERED:

As pointed out at the beginning of this paper, the word allergy implies an "altered reactivity". The Nomenclature Committee of the International Association of Allergology suggest it be defined as "an acquired quantitatively altered capacity of living tissue to react, induced by a specific allergen". Whatever else it is, the allergic reaction is a response to a certain stimulus; this stimulus is usually an antigen-antibody reaction, but whether this is the only possible stimulus remains unknown.

Allergic reactions in which antigen-antibody reactions have been shown to play a major role can be divided into two groups depending upon the time lag between antigenic stimulus and tissue reaction: *immediate type* and *delayed type*.

In the immediate type, antibodies are usually present and detectable in the plasma. When the specific antigen is injected into the skin it gives an immediate wheal reaction. If the serum of a sensitized animal is injected into a normal animal, it conveys the same sensitivity to that animal for varying periods of time; such a passive transfer of sensitivity is known as the Prausnit-

zer-Kustner reaction. This group may further be broken down into two subgroups as demonstrated in the accompanying chart.

In the delayed-type of hypersensitivity antibodies can not be detected in the serum and passive transference is achieved only by the transference of lymphocytes, leucocytes or their extract. The tuberculin test, the response of which takes 12 — 24 hours to develop, belongs to this group and is taken as the prototype.

ATOPY: THE ALLERGIES OF THE FATHERS

Heredity has long been considered of importance in the aetiology of allergic disease. In 1923, Coca proposed the term atopy ("out of the wayness") to designate those clinical allergies believed under hereditary influence — hayfever, atopic dermatitis, and certain cases of asthma.

Many agree that the greater the number of one's ancestors with allergies, the greater one's chance of being allergic and that the individual inherits an allergic predisposition rather than a particular allergic disease. Schwartz, for example, studied bronchial asthma and concluded that it is a Mendelian dominant with failing manifestations so that only 40% who carry the genes develop the symptoms. However, these findings are not universally accepted (32) for Kalver studied 250 allergic families and concluded that the incidence of allergies in the siblings, parents, and grandparents of allergic children is no greater than in groups of the population chosen at random.

NOT BY ANTIGENS AND ANTIBODIES ALONE:

Even in such diseases as asthma and atopic dermatitis in which the antigen-antibody reaction is recognized as playing a predominant role, infection and psychic factors are important and the three may influence one another.

With some types of allergy — especially those of the respiratory tract — infection has a strong association. As has been reported in the instance of *Brucella abortus*, such an infection may actually enhance the production of allergy but, on the other hand, it has been shown that allergy may modify infection for systemic sensitization (non-fatal anaphylaxis) makes mice exceedingly vulnerable to staphylococci. (32)

While it would be strange indeed if chronic allergies did not affect a patient's mental make-up, the reverse is also true for allergic-type reactions, such as asthma, which may be induced as conditioned reflexes (33) and evidence of unconscious motivation has been found in allergic diseases by the psychodynamically-oriented, the very organs selected having a symbolic signifi-

FIG. 3 — ALLERGY

	IMMEDIATE TYPES		DELAYED TYPES
	REAGIN-ANTIBODY	ANAPHYLAXIS-ANTIBODY	(12-24 hrs. or more)
ANTIBODIES	-in serum -heat-labile -L.B.Y. globulins -sensitivity transferred in serum -alpha, beta, gamma globulins -no passive anaphylaxis -induce Prausnitz-Kustner reaction	-in serum -heat stable -Y globulins -in serum -induce passive anaphylaxis -induce Prausnitz-Kunster reaction	-in cells -in (1) leucocytes from peripheral blood of man. (2) leucocyte extract (3) lymphocytes in animals
ANTIGEN	-inhalants, ingestants, contactants -sensitivity develops spontaneously -without affect on many individuals -often haptens -subsequent injection of antigen produces "blocking bodies"	-usually injected -sensitivity usually induced -produces similar affect on most individuals -soluble proteins & carbohydrates -subsequent injection of antigen produces anaphylaxis	-induced by 1. living organisms - fungi bacteria, spirochetes virus. 2. contactants - often haptens combine with lipids of skin 3. antigen & adjuvant (eg. Freund's) -sensitivity develops spontaneously
EFFECT OF ANTIGEN ON SENSITIZED CELLS IN VITRO	-release of histamine	-release of histamine etc.	-cellular injury or necrosis
ASSOCIATED	-eosinophilia -tendency to develop other "atopic diseases" -hereditary important?	-no eosinophilia -no hereditary element	-no eosinophilia? -no hereditary element
CLINICAL PICTURE	-wheal, erythema -no direct correlation between presence or severity of clinical symptoms & quantity of reagin	-anaphylaxis 1. induced-drugs-serum-sickness 2. accidental-insect stings -direct correlation between severity of clinical picture & antibody titre	viral -1. delayed bacterial allergy eg. fungal tuberculin reaction 2. contact dermatitis eg. poison ivy

The immediate and delayed types of allergic reaction are not mutually exclusive. A single antigen can induce more than one type of allergic reaction, as evidenced by trichophyton (the allergen of certain fungus infections), the repeated injection of which can convert an initial delayed response into an immediate one.

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cance. At the turn of the century neuroallergy thrived, (34) but its early bloom was blighted by a too-frequent failure to demonstrate antibodies; however, food allergy still stands implicated in certain cases of migraine headache, epilepsy, speech disturbances, drowsiness, (35) and confusion. Conversely, there is evidence that the site of the emotions lies about the hypothalamus, and that stimuli from this area affect the pituitary and the secretion of cortico-steroids which, in turn, modify the allergic reactions. Thus, allergy may influence infection and infection modify allergy; allergy modify psychological factors, and psychological factors influence allergy.

Many diseases of still undetermined etiology are being studied with a view to discovering their basic mechanism. It is hardly surprising, therefore, that many researchers have turned to the antibody as important in the pathogenesis of many a disease. As Dr. A. McGhee Harvey has pointed out, "Allergy is a unique field in medicine because it deals with a mechanism of disease rather than a specific disease or group of diseases". (36)

If, when we think of the antigen-antibody response, we consider only that fate of a foreign antigen, we are thinking in terms of immunity; if we consider primarily the fate of the body tissues, we are thinking in terms of allergy and hypersensitivity. They are, both, ends of the same spectrum; both result from a defence mechanism engendered by the past and potentially dangerous for the future — a protective mechanism which, like a sword, brings to the animal kingdom both a defence and destruction.

1. Waddell L.A.: Egyptian Civilization, London, Luzac and Co., 1930.
2. Boyd W.C.: Fundamentals of Immunology Ed.2, Interscience Publishers Inc., New York.
3. Cinader B.: Immunochemistry, University of Toronto Medical Journal: xxxvi, 1959.
4. Cass I.M.: Actively Acquired Immunological Tolerance, *ibid.*
5. Gitlin D., Gross P.A.M., Janeway C.A.: The Gamma Globulins and their Clinical Significance I, The New England Journal of Medicine, 260: 1959.
6. Loveless M.H. and Conn J.R.: Distribution of blocking antibodies in human serum protein fraction by electrophoresis — convection; J. Immunol 74: 1955.
7. Coons A.H., Leduc E.H., and Connolly J.M.: Studies on Antibody Production, J. Exper. Med., 102: 1955, Med., 20: 1956.
8. Harris T.N., and Harris S.: Genesis of Antibodies, Am. J. Med., 20: 1956.
9. Ortega L.G., and Mellors R.C.: Cellular Sites of Formation of Gamma Globulin, J. Exper. Med., 106: 1957.
10. Fitch F.W., Wissler R.W., Lavia M., Baker P.: The timing of antigen injection relative to whole body irradiation and the development of circulating antibody, and the splenic histologic reaction in the rat, J. Immunol., 76: 1956.

11. Gitlin D., and Janeway C.A.: Studies on metabolism of plasma protein in nephrotic syndrome I, J. Clin. Invest., 35: 1956.
12. Cohn M., Pappenheimer A.M.: A quantitative study of diphtheria toxin — antitoxin reaction in serum of various species including man, J. Immunol., 63: 1949.
13. Coons A.H.: Discussion in symposium on antibodies, J. Cell, Comp. Phys.: 50, Supp. I, 1957.
14. Lawrence S.H.: The cellular Transfer of Cutaneous Hypersensitivity to Tuberculin in man, A.J.M., 20: 1956.
15. Chase M.W.: The delayed type of allergic inflammatory response, Proc. Coc. Exper. Biol. & Med., 59: 1945.
16. Jerne N.K.: The Natural Selection Theory of Antibody Formation, Proc. Nat. Acad. Sc., 41: 1955.
17. Haurowitz F.: Theories in Antibody Formation in The Nature and Significance of The Antibody Response, Pappenheimer A.M. Jr.; Columbia University Press, 1953.
18. Dale H.H.: Progress in autopharmacology, Bull. Johns. Hopkins Hosp.: 1933.
19. Rocha e Silva M.: Anaphylatoxins and histamine release, Quart. Rev. Allergy, 8: 1954.
20. Ungar G., and Hayashi H.: Enzymatic Mechanisms in Allergy, J. of Allergy, 16: 1958.
21. Mangar J.L., Schild H.O.: Inhibition of anaphylactic reaction, J. Physiol., 135: 1957.
Effect of Temperature on the anaphylactic reaction, *ibid.*
22. Uvnas B.: The mechanism of histamine liberation. J. Pharm. and Pharmacol., 10: 1958.
23. Mayer R.L., Brousseau D.: Antihistamine Substance in Histamine Poisoning and Anaphylaxis in Mice, Proc. Coc. Exper. Biol. and Med., 63: 1946.
24. Halpern B.M.: Histamine et Allergie in Acquisitions Medicals Recentes, Paris 1956.
25. Scroggie A.E., Jaques L.B.: The release of histamine and heparin from isolated perfused liver of the sensitized dog. J. Immunol.; 62: 1949.
26. Weissbach H., Waalkes T., and Udenfriend S.: Presence of serotonin in the lung, and its implication in the anaphylactic reaction; Science, 125: 1957.
27. Erspamer V.: Pharmacology of indole alkylamines. Pharmacol Rev., 6: 1954.
28. Peters G.A., and Silverman J.J.: Role of histamine and acetylcholine in the mechanism of heat allergy, Arch. Int. Med., 77: 1946.
29. Vogt W.: Naturally occurring lipid soluble acids of pharmacological interest. Pharm. Rev., 10: 10.
30. Kellaway C.H., and Trethewie E.K.: Liberation of slow-reacting smooth-muscle stimulating substances in anaphylaxis, Quart J. Exper. Physiol., 30: 1940.
31. Johnson H. H., De Oreo G.A., Lascheid W.P., Mitchell F.: Skin histamine levels in chronic atopic dermatitis. J. of Invest. Derm., 34: 1960.
32. Ratner R.: Silberman D.E., Ann. of Allergy, 10: 1958.
32. Prigal S.S., and Dubos R.: The Effects of Allergic Shock on the Fate of Staphylococci in the Organs of the Mice, Proc. Soc. Exper. Biol. and Med. 93: 1960.
33. Ottenberg P., Stein M., Lewis J., Hamilton C., Learned ' Asthma in the Guinea Pig, Psychosom Med., 20: 1958.
34. Spear F.: Historical Development of Allergy of the Nervous System, Annals of Allergy, 16: 1958.
35. Rowe A.A.: Allergic Fatigue and Toxemia, Annals of Allergy, 17: 1959.
36. Somter M.: On the Impossible, J. of Allergy, 30: 1960.

CLINICAL ASPECTS OF HYPERSENSITIVITY

B. FOGEL, B.A., 6T1.

INTRODUCTION

One of the more important achievements of the medical profession in the last twenty years has been the development of concepts and of knowledge pertaining to hypersensitivity. Hypersensitivity may be broadly defined as an adverse reaction produced by exposure to a foreign substance following an initial or sensitizing contact. The first section of the Journal amply explains this phenomenon. Prior to the 20th century, the word "allergy" did not exist and it was not until the present century that Richet discovered and named anaphylaxis, that Arthus discovered the phenomenon which bears his name and serum sickness was first described and studied by Von Pirquet and Schick. It was also at this time that Hamberger indicated the relationship of antibody to hypersensitivity. However, it was not until the present century that it was recognized that hypersensitivity could produce serious disturbances of the respiratory tract, alimentary tract, urinary, cardiovascular, hemopoietic, ocular and nervous systems; that it was responsible for connective tissue damage and a multiplicity of cutaneous disorders. It was also learned that many innocuous agents could produce serious, often fatal disease by their capacity to induce a hypersensitive state.

Disorders produced by hypersensitivity can be roughly grouped in two categories. First, there are the primary diseases of hypersensitivity, i.e. those in which the disease state is the result of hypersensitivity to agents that are not in themselves harmful but produce symptoms because sensitization has occurred. In this category are the pollens, dusts, foodstuffs, etc., which produce such clinical states as hay fever and asthma. These will be duly considered in a separate section. The second category is comprised of the diseases which are accompanied by sensitization, i.e. those conditions in which disease is produced by agents which in themselves are harmful to the body but in which the disease process becomes intensified as a result of sensitization to the agent. Examples of such agents are micro-organisms and viruses. Hypersensitivity to infection is often referred to as the "delayed or tuberculin" type of hypersensitivity and its role in chronic infections is extremely important inasmuch as it can tremendously intensify the tissue damage and destruction the infecting organism produces. This, in all events, is the reason why individuals suffer from recurring boils and infections and why others are relatively free of such ailments.

The types of damage which can be produced as a result of sensitization were greatly enlarged by the introduction of the sensitizing sulfonamide drugs. This has been intensively investigated by Rich and his colleagues who have studied the tissues of many patients who had hypersensitive reactions to sulfonamide drugs. Rich encountered an association of polyarteritis nodosa and sulphonamide hypersensitivity and he showed that similar lesions could be produced in the experimental animal by injections of foreign sera. Polyarteritis nodosa has also been observed in patients with a hypersensitive reaction to iodine, Aspirin, Dilantin, thioruria, Phenobarbital and antibiotics.

This may be amply illustrated by a patient who developed hypersensitivity to insulin and antibiotics, or so it is thought.

A sixty-seven year old man was admitted to hospital because of uncontrolled Diabetes Mellitus. He was given Lente insulin and subsequently developed an erythematous skin reaction at the site of his injection and also on other parts of his body. There was no history of allergy in his family. It was learned that he suffered from severe skin reactions shortly after the administration of P. Z. I. and would feel generally ill, complaining of severe temporal headaches. Physical examination revealed a chronically ill man. B. P. 180/90, Hb. 11.5 gms.%, normal W.B.C. and differential. Fundi revealed diabetic retinopathy. Peripheral neuritis was also present. Liver function tests were abnormal. Urinalysis showed proteinuria. He was finally controlled with Toronto Insulin but his temporal headaches and skin lesions remained. A diagnosis of a diffuse collagen disease was made. Temporal artery biopsy revealed fibrinoid change compatible with the diagnosis of polyarteritis nodosa. This lesion can probably be explained by a hypersensitive reaction to insulin although the evidence is not wholly conclusive.

The above example illustrates the point that, in every case of polyarteritis nodosa, an etiology should be carefully sought since we know that this life threatening vascular lesion can be caused by hypersensitivity. Experiments also show that with cessation of contact with the agent, the disease process ceases.

Study of sulfonamide hypersensitivity has clearly established the fact that an extraordinary variety of visceral lesions can occur. These include pneumonic consolidation, myocarditis, purpura, agranulocytosis, hemolytic anemia, neurological disorders, arthritis and glomerulonephritis. That the above lesions have been shown to be produced by hypersensitivity reactions to various drugs is of major consequence. It necessitates careful observation of who is re-

CLINICAL ASPECTS OF HYPERSENSITIVITY

ceiving a sensitizing drug so that, where reaction occurs, the administration of the drug is promptly stopped. If not, irreparable damage may be done. Rich cites the example of a physician who took penicillin for an attack of sinusitis and subsequently developed a hypersensitivity reaction of the serum sickness type. Each time penicillin was self-administered, urticaria would result. Malignant hypertension set in and the physician died. Autopsy revealed polyarteritis nodosa. In that such lesions can be produced from common drugs such as Aspirin and a variety of sedatives, the sensitizing properties of therapeutic agents should be kept in mind when you are faced clinically by one of the above-named syndromes in the absence of a specific etiological agent.

COMMON ALLERGIC PHENOMENA

Just how much allergy or hypersensitivity is seen by a physician in general practice? On any basis of computation, it must be considerable, but modified by the interpretation given to a word whose use has got somewhat out of hand. If the word is confined to reactions to a known allergen the number of cases will be much fewer than if it is applied to every set of symptoms which can be of such a nature. Bronchial asthma, hay fever, anaphylactic reactions, to name a few, are allergic phenomena in the true sense of the word. There is, of course, no question about the existence of this allergic phenomenon — the abnormal reaction to something swallowed, touched, inhaled, or given by injection, and it is quite certain that we have not yet seen the limit of its manifestations. There are many examples of acute clinical disorders where the etiology of allergen and the allergic reaction is beyond question. Take for example the anaesthetist who beginning to feel feverish at an operation, took ten grains of aspirin as he had often done before, and suddenly experienced tachycardia and breathlessness. Adrenaline, administered subcutaneously would probably relieve the manifestations of allergy and save his life. Why one dose too many of aspirin sensitized the anaesthetist is not known. From the patient's and from the doctor's point of view it does not matter much. He must never take aspirin again; awkward for the anaesthetist, and awkward too, for the physician who may, in a hurried or unguarded moment, order some aspirin-containing drug to the great peril of his patient. There are less dramatic but equally specific cases: the rare cow's milk-sensitive baby whose lips swell on contact with the first drop; the innumerable contact dermatoses and the multiple drug eruptions.

THERAPEUTIC CONSIDERATIONS

What then does the doctor do about allergy?

The general treatment of asthma, hay fever and other known allergic disorders will be considered in a separate section of this Journal. However, allergy, in its acute and dangerous form, may be met at any moment and the physician should never be without a supply of adrenaline for injection. It is well to have some oral antihistamine handy for less intense allergic reactions. If allergy is suspected the evidence should be searched for by questioning and history-taking rather than by prick, scratch or patch test, bearing in mind that such tests are not always harmless. If an unquestionable allergen is found, it is of importance to stress to the patient that the essential part of treatment in the present state of knowledge is to avoid the allergen rather than to hope that drugs or graduated injections will abolish or counteract susceptibility. As a rule the patient must learn to live with his disability, accept and use to the full whatever palliation there is to offer and not waste time and money seeking a non-existent cure.

ANAPHYLACTIC REACTIONS.

Some consideration should be given to anaphylactic reaction which is characterized by the sudden onset of dyspnoea and shock due to an antigen-antibody union. Occasionally it is an accident which could not have been foreseen but usually with sufficient care, such reactions are avoidable. Well known causes of anaphylactic reactions are penicillin, sera, and extracts of allergens used in the investigation and treatment of hay fever and asthma. These account for the vast majority. Such reactions may also occur from bee or wasp stings and exceptionally from foods such as shell-fish and nuts, and in infants, from egg or milk. Also they have very rarely followed the injection of insulin, corticotrophin and streptomycin. The symptoms may come on with alarming suddenness or may be delayed up to about half an hour. The earlier the onset, the more severe and dangerous will be the reaction; most deaths occur within ten minutes and dangerous reactions are very rare after thirty minutes. There may be sudden collapse and rapid onset of unconsciousness. More often there is first a feeling of apprehension, a pounding headache, throbbing in the ears, sweating and giddiness. Shock is a prominent feature in most cases.

The reduction and prevention of anaphylactic reactions are based on the following principles: the avoidance of the use of allergenic substances except when essential and the taking of special precautions when treating a patient with a personal or family history of any of the allergic diseases. A person cannot be allergic to a substance with which there has been no previous

CLINICAL ASPECTS OF HYPERSENSITIVITY

contact, but in allergic patients the degree of previous contact may have been slight and often forgotten except on specific questioning. It is a fundamental rule that intravenous injections of allergenic substances should not be given when intramuscular or subcutaneous injections will suffice.

Anaphylactic reactions from penicillin are becoming more common and warrant some discussion. The predisposing factors are of course the widespread use of penicillin therapy and the allergic background of some ten per cent of patients. Sensitization and allergic reactions have been shown to occur as the result of previous topical applications such as ointments and creams, from aerosol therapy, from oral administration in the form of lozenges or capsules, or from parenteral therapy, and from the drinking of milk from cows treated with penicillin for mastitis. Anaphylactic reactions occur most commonly when penicillin is administered at an interval of weeks, months or longer.

Serum sickness due to horse sera is of course a common occurrence and patients with a personal or family history of allergic diseases should be immunized with tetanus toxoid. When anaphylactic reactions occur, treatment must be immediate and consists of giving adrenaline subcutaneously and cortisone if needed.

VISCERAL LESIONS

After a cursory consideration of some of the better known allergic phenomena, we now turn our attention to the visceral lesions that are definitely known to be on a hypersensitive basis.

It was demonstrated by Harkavy that *pneumonitis* can result from hypersensitivity. He showed that there were transient pulmonary infiltrations of inflammatory cells in association with such allergic diseases as asthma, urticaria and others. It has been established that *myocarditis* can occur from hypersensitivity. Tissue studies have shown that hypersensitivity can produce focal inflammatory infiltrations of the myocardium.

Perhaps, of all the visceral diseases supposedly of hypersensitive origin, *glomerulonephritis* has been most extensively investigated. That glomerulonephritis may be on a hypersensitive basis has long been suspected. After an infection with streptococcal type 12 organisms, nephritis occurs only after a lapse of time sufficient to permit an active development of antibody and of hypersensitivity. From the studies of different investigators, it now seems clear that glomerulonephritis may be induced immunologically in

the laboratory animal by three different mechanisms: by the introduction of anti-whole-kidney antibodies, by the intravenous injection of foreign protein, and by the injection of bacteria or their products. Although the disease in laboratory animals is induced in a highly artificial manner, it has been shown by some investigators that clinical and pathological features of the experimental disease bear a close resemblance to those seen in human glomerulonephritis. It has also been shown that there are circulating antibodies in glomerulonephritis and it is thought that these antibodies may be auto-antibodies. The search for circulating auto-antibodies in glomerulonephritis and the nephrotic syndrome in man has been carried a stage further by Liu and McCrory. They used a specific hemagglutination as the indicator system and a tryptic digest of human kidney serum as the antigen. Seventy-one per cent of patients with acute nephritis were found to have anti-kidney hemagglutinin titers of 1:20 or higher, and 89% with the nephrotic syndrome, and active disease, had elevated antibody levels. No healthy person tested had a titer of 1:20 or above, and negative results were also obtained in renal disease not associated with glomerulonephritis.

Several studies that have been made on glomerulonephritis seem to have one feature in common which suggests the presence in the circulation of a substance or substances directed against some component of renal tissue. Further studies in the experimental and human disease indicate this component is closely related to the glomerular basement membrane. Studies with foreign protein nephritis (i.e. injecting foreign protein into a laboratory animal previously sensitized with it) have brought to light the following suggestions as possible factors in the pathogenesis of the disease; that the foreign proteins either localize in the basement membrane long enough to combine with the antibodies produced in response to it, thereby producing tissue damage, or that the foreign proteins in some way affect the membrane so that the now-altered structure becomes auto-antigenic. Evidence points to both possibilities but as yet there is nothing conclusive. In human glomerulonephritis, the evidence strongly suggests that a previous streptococcal infection is responsible for the majority of cases of acute nephritis and that the nephritogenic streptococci are involved in an immunologic reaction within the kidney. We see therefore that hypersensitivity is intimately related to glomerulonephritis although the exact pathological pathway is still unknown.

COLLAGEN DISEASES

In recent years a group of diseases has been

collectively referred to as *the collagen diseases*. They exhibit a wide variety of clinical and pathological manifestations that can be produced by the anaphylactic type of hypersensitivity. Under this label are included rheumatic fever, rheumatoid arthritis, systemic lupus erythematosus (S.L.E), polyarteritis nodosa, thromboangiitis obliterans, scleroderma. It is not our purpose to discuss the symptomatology and pathogenesis of these disease processes. For this, the reader is referred to an excellent article on the pathology and pathogenesis of the collagen diseases by Movat appearing in a recent article of the *CANADIAN MEDICAL ASSOCIATION JOURNAL*.

For some of the above diseases, an allergic etiology was postulated as early as 1902. It was not however, until the publications of Klinge in the late 1920's and early 1930's that all of them were grouped together as allergic. Klinge considered fibrinoid damage to connective tissue as a lesion specific to tissue allergy and his experiments and statements have stimulated further research in this field. However, all that can be concluded from such investigation is that the evidence for the role of an antigen-antibody reaction in the pathogenesis of the collagen diseases is highly suggestive. Ogryzlo has summed up data which indicates that the pathogenesis of systemic lupus erythematosus is related to an immunochemical disturbance in which an abnormal antibody-producing mechanism may be the most important factor:

1. *Increased production of gamma globulins.* Using the fluorescent antibody technique, it has been shown that normal tissues and ordinary acute inflammatory lesions contain more albumin than globulin, whereas in the lesions of S. L. E., rheumatic fever, etc., there is a greater concentration of globulin.

2. The frequent occurrence of biological *false positive serological tests* for syphilis.

3. *The L. E. cell phenomenon.* Abnormal immunologic reactions involving the patient's own cells occur with great frequency in S. L. E. They form the principal basis for the suspicion that autoimmune processes participate in the pathogenesis. Groups of antinuclear and anti-cytoplasmic antibodies are found in the sera of these patients. One of these antibodies reacts specifically with desoxyribonucleohistone and is responsible for L. E. cell formation. The abnormal immunologic reactions in S. L. E. have not been incriminated in the pathogenesis. However, their existence suggests that S. L. E. may be one manifestation of an abnormal immunologic response.

4. The occasional demonstration of an *abnormal circulating anticoagulant*.

5. The occasional *presence of autoantibodies* for red cells.

6. The frequent *sensitivity* of these individuals to sunlight, blood transfusion, chemotherapeutic agents and antibiotics.

7. The more recent *observation of syndromes* resembling S. L. E. which appear to have been precipitated by the administration of hydralazine in the treatment of hypertension. The latter point may be amply illustrated by the following example:

A 47 year old white woman was admitted to Hotel-Dieu Hospital in March of 1954 because of severe hypertension and slight cardiac failure. Physical examination revealed a blood pressure of 220/132 mm. Hg., left ventricular hypertrophy. Hb. level was 10.4 gms.% W. B. C. 5250, normal differential. P.S.P. showed 16% excretion in 80 minutes. In June of 1954 she was given Hydralazine (213 mgms/day). She remained asymptomatic, taking Hydralazine in combination with other antihypertensive drugs until February 1956. At this time she developed tenderness in her hands and elbow joints in addition to asthenia and a weight loss of 15 lbs. She discontinued her medication in March 1956. In April 1956, she was admitted to hospital with pallor, asthenia, malaise, nausea, vomiting, loss of weight, clay-coloured stools, dark urine and R. U. Q. pain. She had a butterfly rash on her face, hypertension (220/110), slight pretibial infiltration, cervical and axillary lymphadenopathy, hepatosplenomegaly. Pain was present on motion of her knee or left elbow. E. S. R. was 33 mm., Hb. 8.5 gms.%. Eosinophils numbered 320 per c. mm. of blood. Liver function tests were abnormal and there was an increase in the gamma globulin fraction of the serum proteins. Bone marrow aspiration was normal. At no time, however, were L. E. cells found.

This case fits the clinical picture of a collagen-like disease due to long-term use of hydralazine. That this is due to hypersensitivity, is an attractive hypothesis. At present, the pros and cons are still being debated. Although it is clear that antibody-antigen interaction is capable of producing serious tissue damage, just how it accomplishes this in the collagen diseases is completely unknown. One can say only that hypersensitivity seems to be implicated.

AUTO-IMMUNITY

It is generally accepted that species - homologous tissue components are not antigenic. Nevertheless, autoimmune mechanisms of pathogenesis have long been suspected in a number of pathological conditions especially in those referred to as the collagen diseases. Autoimmune mechanisms have been suggested for certain types of thrombocytopenic purpura, hemolytic anemia, acquired agranulocytosis, leukopenia, encephalomyelitis, multiple sclerosis, amyotrophic lateral sclerosis, Hashimoto's disease, sympathetic ophthalmia, ulcerative colitis and for certain forms of chronic hepatitis. A vast literature has appeared on the experimental induction of immunological damage simulating the lesions of acute glomerulonephritis, polyarteritis

CLINICAL ASPECTS OF HYPERSENSITIVITY

nodosa, multiple sclerosis and thyroiditis but the actual demonstrations of such immune mechanisms have been few and inconclusive. Only in the hematological diseases such as the leukopenias, hemolytic anemias and certain thrombocytopenias have true circulating antibodies been demonstrated.

It has often been suggested that any process causing abnormal destruction of cells might under certain circumstances evoke an auto-antibody response. On this hypothesis, a wide variety of tissue injuries might be involved and an equally wide range of cell components develop pathological antigenicity. It is classical teaching that lipids released from cells damaged in the course of syphilis become autoantigens evoking the production of antilipid antibodies detected in the Wasserman and other serological tests. Similarly, cell proteins, nucleoproteins and particulate components may act as auto-antigens if they are released by destructive processes from cell interiors into the blood stream and so come in contact with cells of the reticuloendothelial system. However it is still a matter of speculation as to whether such cell components must be altered so as to become antigenic, and if so, what changes are involved.

THYROIDITIS

Witebsky has shown that saline extracts of thyroid glands incorporated into Freund adjuvants (lanolin, acid-fast material, etc.) are antigenic not only for animals of homologous species but even for the individual animal from which the thyroid extract was obtained. Marked histological changes found in the thyroid glands of the immunized animals closely resemble the pathological changes occurring in chronic thyroiditis, circulating antibodies can be demonstrated by the Fluorescent test. These antibodies are directed against human thyroid extracts, including extracts of the patient's own thyroid gland. For these reasons it is proposed that auto-sensitization plays an important part in the pathogenesis of some forms of chronic thyroiditis in man.

In Roitt's series, circulating antibodies were found in 83% of primary myxedema, while the corresponding figures in thyrotoxicosis, non-toxic colloid goitre and thyroid cancer were 63%, 33% and 32% respectively. The highest titres are found in Hashimoto's disease while titres in other thyroid diseases are, generally, far lower. It has been suggested that auto-antibody levels in carcinoma of the thyroid are sufficiently low enough to make this finding a useful adjunct in the differential diagnosis between Hashimoto's disease and thyroid malignancy. Thyroid auto-anti-

bodies are found at least three times more often in patients with colloid non-toxic goitres than in the general population of comparable age groups, and their incidence is six times higher in thyrotoxic patients. This local abnormality in the thyroid gland appears to play an important role in the initiation of thyroid auto-immunity.

SYSTEMIC LUPUS ERYTHEMATOSUS

Of the large group of illnesses in which disturbances of immunological processes have repeatedly been observed, systemic lupus erythematosus may be selected as an outstanding example. S. L. E. classically runs a fluctuating clinical course, with involvement of multiple organs and tissues in a progressive inflammatory process. The discovery of tissue auto-antibodies by the agglutination of tanned red cells in some cases of S. L. E., the discovery of the L. E. cell by Hargraves and the identification of the L. E. factor as a gamma globulin – possibly antibody to human leukocytes – give further support to the hypothesis that S. L. E. may have an auto-immune pathogenesis.

It has been suggested that the basis of the usually progressive character of diseases in the group of conditions showing auto-immune reactions, is a failure of some sort of protective mechanism which normally functions to prevent the ill effects of auto-antibody production. In this way, a self-perpetuating disease condition could be engendered. However, there is still uncertainty as to which cellular components are antigenic in any given case, what range of antibodies is present, and how damage to the tissues involved has been produced.

CONCLUSION

It is obvious that there are numerous problems remaining which must be solved before the total phenomenon of hypersensitivity is fully understood. Further investigation and experimentation is now in progress to solve these problems and it is hoped that their solution will lead to a better understanding and, hence, to a better management of the hypersensitive state.

ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. William Spaulding for his suggestions and assistance in the preparation of this paper.

CLINICAL ASPECTS OF HYPERSENSITIVITY

1. Annals of Int. Medicine; Vol. 52, No. 4, 1960.
2. The Practitioner; Vol. 184, No. 1102, 1960.
3. Annals of Allergy; Vol. 17, No. 5, 1959.
4. New England Journal of Medicine; Dec. 10, 1959.
5. Archives of Int. Medicine; Jan. 1958.
6. Brit. Med. Bulletin; Vol. 16, May 1960.
7. Rich, A. R. and Gregory, J. E.; Bull, Johns Hopkins Hosp.; 72, 65; 1943.
8. Ibid.; 75, 115; 1944.
9. Ibid.; 81, 312; 1947.
10. C.M.A.J.; Vol. 83, Oct. 1960.
11. Hamilton, J. D. and Frommes, N. E.; Am. Journ. Path.; 30, 127, 1954.
12. The Medical Graduate; Vol. 4, 1957-58.
13. Opie, E. L.; Medicine; 15, 489, 1936.

BOOK REVIEW

SYNOPSIS OF PATHOLOGY;

W.A.D. Anderson, M.D.

First published in 1942 as a volume "intended to fill a gap which has existed between the very elementary manuals of pathology and the abundant excellent larger textbooks", this standard text, now in its fifth edition, has lost none of its original intent. Nor has it lost any of the quality and usefulness which first popularized it with student and practitioner. It has undergone only updating made essential by the rapid progress of medical research.

All chapters have received attention and revision has been made where the subject is relatively important, of current interest, or where there has been recent new information. For example, pulmonary cancer with its rapidly increasing incidence has received more consideration than before. The changing patterns of the infectious diseases and diminishing incidence of old scourges such as tuberculosis and malaria are discussed. The field of virology is covered in the light of research into the fundamental nature of the virus and the pathology it causes.

Newly recognized diseases or syndromes have been included as well as altered aspects of those known previously. Included, to mention but a few, are pulmonary alveolar proteinosis, aldosteronism, carcinoid syndrome, and familial chronic idiopathic jaundice. New information and understanding is given of histoplasmosis, toxoplasmosis, hemaglobinuric nephropathy, nephropathy of potassium deficiency, amniotic fluid embolism, viral hepatitis and many more. Practical cytological diagnosis of neoplasms is dealt with and numerous tumors have been renamed or reclassified.

Vascular disease, subject of intense study, has been revised to contain important new concepts of the role of endarterial thrombi in the pathogenesis of atheroma and of intimal vascularization and hemorrhage in atherosclerotic occlusions. The field of endocrinology, particularly the adrenal cortical hormones and their role in growth, inflammatory and metabolic processes, is elucidated. The pervasive importance of hypersensitivity is realized and a concept of the "collagen diseases" has been developed. The importance and cumulative effects of irradiation are discussed and emphasized with respect to our atomic age.

The size of the volume is maintained despite the extensive revision and inclusion of material. The text illustrations, a distinct feature of the work, number over four hundred. The binding has changed from the old red and blue cloth to a handsome maroon leather making it decorative as well as informative.

Almost every student of medicine has been advised at one time or another to purchase this jewel, something which connotes general approval and acceptance of it. Practically speaking, it is *complete* for most of us and, although no pretender, would serve as a reference to all but the most discriminating academician. If your need in pathology is an informative, fat-free and lucid manual, heed the clarion call of two decades and "pick up an Anderson".

L. E. S.

5th Edition, 1960:

C.V. Mosby Co.; 876 pp.; \$ 9.25.

THREE COMMON ALLERGIC DISEASES

R. KINGSLEY GILL, 6T1.

HISTORICAL:

The history of hypersensitivity readily reveals the fact that we are dealing with but an infant in the family of medical science. But if the medical world has been slow to recognize its existence, mothers have for centuries noticed that their infants were "poisoned with cow's milk or eggs" and that coryza or asthma occasionally followed animal contact. Possibly Hippocrates had a faint inkling of allergic phenomena when stated in his sixty-fourth aphorism that "It is a bad thing to give milk to persons having headache."

Floyer (1648) is to be credited with the idea that asthma is caused by bronchial constriction and edema. The common causative agents of hay fever were recognized by Blackley and Dunbar, who, in 1865 and 1905 respectively, incriminated pollens, animal danders and dusts. From 1900 to date, the American Schools must be credited with the major steps in the understanding of hypersensitivity. This is probably due to the fact that ragweed is non-existent in the United Kingdom and Europe and the Continental people generally do not spend much of their time indoors, so that the allergens such as pillow feathers, dust and pets are not too great a problem for them.

INTRODUCTION:

The purpose of this article is to enable the reader to have a very practical grasp of the problems in diagnosis and treatment of the commonest allergic diseases, namely, bronchial asthma, hay fever (pollenosis) and contact dermatitis (dermatitis venenata). The role of the general practitioner in relation to the problem of overall patient care will be discussed. No attempt will be made to include aspects not directly related to the patient's welfare.

Asthma and hay fever pose a double problem. The first is to recognize the disease for what it is, which is generally not difficult. The second and most frustrating problem to most physicians is the determination of the actual causative agent(s) involved in the individual case. Since these are usually chronic illnesses, and since (only 20-40% of these patients will ever achieve absolute relief even with the best of treatment, the long-term aspects of inconvenience, cost, and discomfort that the patient is willing to tolerate must all be carefully considered and discussed with him before treatment is begun. He has the final decision as to whether he wishes full-scale treatment or not. However, he should be told of the complications, e.g. the possibility of asthma and respiratory infections following unchecked hay fever, and

emphysema being a possible sequelae of long term asthma. Since there is no "one-drug-cure" for these illnesses every possible means to reduce the patient's disability should be considered. The entire care of the patient, with the exception of skin tests and the preparation of the vaccines, can be the job of the general practitioner.

ASTHMA

ETIOLOGY:

Asthma is a symptom complex, resulting from the interplay of many forces. In many asthmatics there is a demonstrable constitutional predisposition to the so-called allergic diseases. Foods (coca, milk, eggs, strawberries etc.) and inhalants (moulds, pollens, dusts) are the most commonly implicated. In others infection is of prime importance, while in still others psychological forces are culpable. Indeed, asthma may be considered as both a psychosomatic and a somatopsychic disease.

SYMPTOMS AND SIGNS:

The average attack of asthma is paroxysmal and recurrent. The attacks frequently occur in the morning hours, waking the patient with dyspnea, choking, coughing and wheezing. He assumes the orthopneic position. He may hold onto the back of a chair or table in an effort to bring into play the accessory muscles of respiration. He becomes anxious and somewhat panicky, insisting that the window be opened so that he may get more air. He may be found sitting in front of a window and is rarely found lying quietly in bed. There is usually a sense of tightness across the chest. The wheezing, usually expiratory, may be audible without the use of a stethoscope. The dyspnea is expiratory. The cough is dry, hard and exhausting. As the patient's condition improves, (taking a few minutes to hours or even days) the cough becomes productive of a thick tenacious sputum which later assumes a more liquid consistency. It should be noted that the only evidence of asthma in a child may be a persistent cough, possibly associated with a slight rise in temperature. This picture may be mistaken for bronchopneumonia if the examination is cursory.

The *physical findings* are widespread rhonchi, with a prolonged expiratory phase. In older people, especially those cases complicated by chronic bronchitis and/or emphysema, there may be residual wheeziness with a few rhonchi present at all times, possibly with the addition of some râles. Usually, the lungs are remarkably clear between attacks.

THREE COMMON ALLERGIC DISEASES

Occasionally, it will be difficult to distinguish bronchial asthma from "cardiac asthma", bronchitis and emphysema, or from respiratory infection. Signs which rule for, or against, asthma are:

- a) asthmatic lung signs and symptoms are always diffuse and bilateral — never localized.
- b) asthmatic rhonchi are almost exclusively expiratory — those in "cardiac asthma" and infection are often inspiratory as well.

Additional findings, such as eosinophilia (often 7 - 10%), Curschmann's spirals (small bronchial mucous casts) and the finding of many eosinophils in the sputum using Wright's stain, are neither practical nor necessary procedures in general practice.

THE HISTORY:

The importance of a thorough history cannot be too greatly emphasized. The tracing of the causative agent(s) may well reveal the doctor's ingenuity, or lack of it. In the history, be especially aware of seasonal episodes, circumstances and locality at the time of onset, periodicity of attacks, and methods of relief (remarkably enlightening in many cases). Some points to notice are:

- (a) *seasonal variation* — freedom from summer attacks is common in food allergy.
- (b) *environment* — beware of occupational causes.
- (c) *frequency of attacks* — regular two to eight week recurrences are common in food allergy.
- (d) *relief methods* — relief on leaving the house may incriminate house dust. Curative hot drinks may reveal allergy to cold. Childish food dislikes are often indicative.
- (e) *familial history* — the capacity to become hypersensitive is inherited in a large percentage of cases.
- (g) *aggravating factors* — a walk in the woods may indicate tree pollen.

The history of food allergy is quite typical. The child, often eighteen to twenty-four months old, develops a "cold" which preceeds or accompanies the asthma. Attacks recur from two to eight weeks, and in summer, relief may be noted. Food allergy is found most often in children, and these cases may be difficult to recognize and manage. It is less common in adults, and, when present, the patient can usually make his own diagnosis. One should be careful to ask indirectly about certain foods to avoid taste preferences, e.g. in questioning about omelettes you may be thinking specifically of egg.

Bacterial (intrinsic) allergy occurs in infants and the middle-to-older age groups. Typically these start with a 2 - 3 week head "cold" which

"moves down" to the chest and then merges into asthma. Subsequent attacks will become more frequent and the initial "cold" of shorter duration.

Summer involvement suggests pollens and moulds, winter attacks connote infection, and indoor attacks bring to mind dusts and animal danders. Strong odours, fumes, chronic upper respiratory infection, smoking, humid climate with rapid temperature change, and endocrine alterations as in menstruation and pregnancy frequently act as "trigger" mechanisms to an attack. In the majority of asthmatics, there is a combination of extrinsic and intrinsic factors which produce the condition.

Skin tests should be considered as minor additional assistance and be interpreted only in the light of the history. In unskilled hands, these tests may be erroneously interpreted and frequently lead to more confusion than help. If a series of skin tests and long term hyposensitization treatment are considered it is best to consult an allergist. The decision must be made between the physician and patient as to whether the severity of the case warrants the time and cost of skin testing and hyposensitization.

Skin tests in many cases, may aid in finding hitherto unsuspected causes of extrinsic asthma. They are not of much value in cases of food or bacterial allergy and it should be noted that 25% of normal individuals will give false positive tests. If symptoms are severe enough to warrant prophylaxis, a complete history, with a list of the indicated agents is sent to an allergist. The number of tests performed will depend on the indicated agents and the known causative agents in the particular locality. The agents giving positive skin tests, plus specific recommendations, are sent back to the practitioner.

TREATMENT

Hyposensitization

From the recommendations of the allergist or allergy clinic, a pharmaceutical house is asked to prepare a treatment extract (5cc) containing all the agents indicated by the history and the positive skin tests. If the patient is reported as being very sensitive, the course of injections begins with a 1:25,000 dilution, whereas less sensitive patients may begin with a 1:5,000 dilution. Ignore any dosage schedule given with the vial.

By subcutaneous injections, 0.05 cc. of the extract is given the first week, 0.10 cc. the second and 0.15 cc. the third week. Include one minum of 1:1,000 epinephrine in the same syringe each injection. These are continued until definite improvement is reached whence the dose is tapered slowly, giving injections every second and, then, every third week. Injections should

be tried for 3 years and continued for at least one year following the last attack before a trial of complete withdrawal is suggested.

If a local reaction greater than one inch occurs, or systemic symptoms become obvious, reduce the next dose to half, or less, from which point the dosage is, again, gradually increased. Each patient should be treated individually, the doctor's judgment being superior to any rigid schedule. Additional precaution may be exercised by keeping the patient in the office for 15-20 minutes following injection to see if any undue reaction occurs.

Hyposensitization in food and bacterial allergies has been found of value in only a few cases.

Drug Therapy

To ward off or alleviate acute asthmatic episodes, various pharmacologic agents are employed. Their main use is plaitive but, in chronic cases, they may be taken daily of necessity. In bacterial asthma, antibiotics are essential for early control but the use of *penicillin must be avoided*. Bronchodilators such as Aminophylline (enteric-coated tablets) and adrenaline (subcutaneously) are most efficacious in the acute attack, and both may be administered by the patient. Subcutaneous adrenaline is a good office procedure but unreliable when left to the patient alone. Nebulizers, containing bronchodilators and enzymes may give immediate relief, but overuse may lead to severe bronchitis. Liquefaction of mucus plugs by potassium iodide or ammonium chloride is often helpful, but even more so is intravenous therapy. An electric fan may do much to relieve air hunger. Reassurance is important, but the greatest reassurance is the prompt institution of effective treatment.

HAY FEVER:

This is the seasonal type of allergic rhinitis. Many of the principles mentioned in the diagnosis and treatment of asthma pertain also to this disease. The main differences between the two diseases are as follows:

- (a) Etiology: The allergens responsible for hay fever are more readily identified as a rule, and for all practical purposes, are the pollens of trees in Spring, grasses in Summer, and weeds (especially the ragweed family) in the Fall. The spring and summer varieties often cause minor irritation and are short lived (one to two weeks). Thus the patient is often satisfied with symptomatic treatment.
- (b) Skin tests and hyposensitization form an extremely important and valuable type of therapy in hay fever.

SYMPTOMS:

The first attack is often mistaken for a common "cold". However, in the following years when attacks rarely vary in date of onset by more than a week from the previous year in the same locality, diagnosis becomes easy.

Sneezing is usually the first symptom, often in paroxysms, and later a serous discharge from the edematous nasal mucosa results. The eyes become watery and itchy, and the conjunctivae red. A feeling of malaise soon ensues, and signs and symptoms of asthma may follow.

TREATMENT:

During the acute attack, symptomatic treatment is the only therapeutic measure available. Avoidance of the allergen should alleviate the condition. Air-conditioning, or simply remaining indoors often helps. Antihistamines are of benefit, but one should remember their sedative action. If these will not alleviate the condition, short-term steroid therapy is permissible.

When the acute attack has subsided, there is a place for hyposensitization. During the acute attack, it should not be attempted, for it may produce severe exacerbation.

CONTACT DERMATITIS:

SYMPTOMS, SIGNS AND HISTORY:

Contact Dermatitis is the most frequent cause of skin eruption. The acute onset of a well-demarcated, superficial, "red rash" followed by edema, vesiculation, crusting and, in chronic cases, a tough thickened covering called lichenification are the progressive (but variable) steps in this disease. It is of utmost importance to remember that lesion starts at the point of contact with the allergen; therefore, one must question the patient carefully for the point of origin. For the same reason, exposed skin areas, especially the backs of the hands, are most often involved. Probably the second most important point is to remember that since this is a delayed type of hypersensitivity, periods from hours to two weeks may have elapsed since the actual moment of contact. One should be continually listening for identical circumstances in repeated attacks and enlist the patient's aid in this detective work. Poison-ivy dermatitis, generally speaking, is the plague of children, whereas occupational and cosmetic agents affect the young adult. Dry and fair-skinned persons are more susceptible; heredity seems to play a small part if any. The palms of the hands are rarely involved.

Clinical Examples:

Mr. Jones works as a machinist. Three days ago he switched to a new machine, and the job involves handling cutting oil. Both hands and

THREE COMMON ALLERGIC DISEASES

forearms have been blotchy red and itchy since this morning. The oil is the causative agent.

Jane Smith bought a school ring three months ago. During the past week inflammation began under and around the ring, and has spread up the forearm. She found today she was unable to remove her ring. The nickel of her ring is responsible.

Mrs. George, who returned to secretarial work three weeks ago after raising a family, has for the past few days been bothered by redness, puffiness and itching on the dorsum of both feet and behind both knees. Nylon is incriminated.

It is simple to remember the diagnostic triad of superficial redness, itchiness, and exposed location. Two items are of special interest: (a) An extremely wide variety of animal, vegetable and mineral products have been incriminated and therefore one should be broad-minded in history-taking, at the same time remembering that soaps, cosmetics, synthetics, and occupational chemicals (particularly oils and tars) are most frequently involved. (b) Any affected individual is susceptible to one or very few agents, and this should make the doctor optimistic of success.

DIFFERENTIAL DIAGNOSIS:

This condition must be differentiated from primary irritation. To primary irritants, all individuals react, and there is no evidence of changed reactivity of the skin to the substance following a previous exposure. It may be difficult, at times, to distinguish between contact and seborrheic dermatitis; however, contact dermatitis is more acute in onset, not associated with greasy scaliness, and is not common in the scalp. Foot involvement, which is quite common has often been misdiagnosed as fungus infection. At times, atopic dermatitis closely simulates contact dermatitis. Patients with atopic dermatitis usually give a personal or family history of allergic disorders. Although reagins are found in their serum, in only a minority of cases can allergens be shown clinically to contribute to the disease, or produce flare-ups in its course.

SPECIFIC DIAGNOSIS:

When the doctor is reasonably sure he has identified the agent, a simple patch test can be done by any general practitioner using the suspected allergen.

The allergen should be placed in the uncut, hairless skin of the arm or thorax, covered with a gauze and cellophane tape (adhesives may give a false positive) and read in forty-eight hours. The following precautions should be taken:

1. Never test during an acute phase.
2. Large blister-like reactions indicate a primary irritant.
3. Intense local itchiness within forty-eight hours is the signal to remove the covering. If left, a general reaction may result.

TREATMENT:

"It is much safer to undertreat than overtreat" is the motto that should be followed. This disease is normally self-limited to one to four weeks after the last contact.

Avoidance: this is the only sure treatment. If avoidance is impossible, a protective silicone cream should be applied before exposure, and washed off with soap and water as soon as possible after exposure.

In mild cases, one should avoid soap and apply a non-irritating substance such as Nivea cream, or calamine lotion containing 1% camphor for relief of itchiness. Compresses for thirty minutes three or four times daily will dry up the lesion. If infection is superimposed one may add such a substance as Vioform 1% in a cream base. Sedation will prevent restless sleep and thereby diminish unconscious scratching.

BIBLIOGRAPHY

- Rowe, A.H. and Rowe, A. H. Jr.; "Bronchial Asthma: Its J.A.M.A., 172: 16, Apr. 16, 1960.
- Segal, M.S.; "Current Status Of Therapy In Bronchial Asthma" J.A.M.A., 169:10 Mar. 7, 1959.
- Cooke, R.A.; Allergy in Theory and Practice; W.B. Saunders Co., Phila. 1947.
- Grollman, A.; Pharmacology and Therapeutics; Lea and Febiger, Phila. 1960.
- Cecil, R.L. and Loeb, R.R.; A Textbook of Medicine; W. B. Saunders Co., 1959.
- Pillsbury, E.M., Shelley, W.B. and Kligman, A.M.; Dermatology; W.B. Saunders Co., Phila., 1956.
- Stewart, P.T.; "Treatment of Dermatitis Venenata"; Milit. Med. 125:4 Apr. 1960.
- Harrison, T.R.; Principles of Internal Medicine; McGraw-Hill Book Co., Toronto, 1958.

TOLBUTAMIDE IN THE TREATMENT OF THROMBOANGIITIS OBLITERANS

Inder Singhe, N.S. Brasa: The Lancet, Sept. 17, 1960.

Thirty-six patients, all Indian males between 25 and 42 years, with thromboangiitis obliterans were treated with tolbutamide. In 2-4 weeks,

there was complete relief of intermittent claudication and rest-pain in 34 patients., but the neuritic pain in 2 patients did not respond. When the tolbutamide was discontinued the relief persisted for 1-7 weeks. Three cases which have been on maintenance therapy have been kept in clinical remission for over two years.

One of Moliere's characters states that "Everyone dies of the remedy, not the malady." (1) Although death from drug allergy is rare, nevertheless it is important to realize that detrimental reactions do occur, and to be able to recognize and assess them. This paper will briefly discuss a definition of drug allergy, the mechanisms involved, some common and uncommon manifestations and means of exposure, and finally, something about diagnosis, methods of safe administration, and treatment of reactions if they should occur. Rather than deal with many examples and minute details, this discussion will confine itself mainly to penicillin reactions from which the principles of the phenomenon may be elicited.

DEFINITION.

Allergy may be defined as an altered or heightened way of reacting to an antigen or hapten; it is an exaggeration of the body's normal mechanisms of antibody formation. (13) The detrimental affects are produced not by the presence of either antibody or antigen in large quantity but rather are due to the antigen-antibody union either in the circulating blood, or on the inside of tissue cells. When assessing the safety of readministering a drug, it is especially important to distinguish allergic reactions from side effects or toxic effects, which are pharmacologic actions other than those for which the drug was given, and from idiosyncrasy or unusual susceptibility to pharmacologic action. For instance, with a first dose of aspirin, a few patients develop tinnitus which is considered an idiosyncrasy. Other patients tolerate the first administration well but develop bronchial asthma after the second dose. (13) This is an allergic reaction. It is not intensified by increasing the dose, as is tinnitus with a larger dose of aspirin. Often, although the reaction to a drug is recognized clinically as an allergic type, antibodies cannot be demonstrated so that the allergy remains only as a hypothetical entity.

MECHANISM.

The majority of drugs are not proteins but simple chemical substances which are not, by themselves, antigenic, but there has been much evidence both experimentally and clinically that chemical compounds have affinity for proteins and form chemical combinations which elicit allergic reactions.

Landsteiner and his associates (1) have shown that antibodies are found against simple sub-

stances such as arsenilic acid by chemically linking it *in vitro* to protein and then injecting the conjugate into rabbits. The rabbit serum gave a positive precipitin test with the conjugate of arsenilic acid and original protein, or with a conjugate with another protein, but not with the original protein plus a hapten of different chemical composition. (1) It is therefore the drug hapten which confers specificity upon antibody formation and sensitivity reaction.

Clinical allergy to a drug may be of either the immediate or the delayed type, or it may present as a combination of both types as is sometimes found in penicillin reaction. In the immediate sensitivity reaction, within a few minutes of administration, there is dilation of capillaries and arterioles, prominent erythema and edema, and little cellular infiltration. Circulating antibodies can be demonstrated; these may be precipitating antibodies found mainly in the gamma globulin fraction, or non-precipitating antibody called reagin, found in the alpha or beta fraction. (13) Passive transfer of sensitivity is possible by injection of serum into a non-allergic host.

On the other hand, in a delayed reaction which is usually maximum in 24-72 hours, there is little edema, but rather an inflammatory change with predominant mononuclear infiltration. Passive transfer is not obtained with serum but at least in some cases it may be produced by injection of live cells. Precipitin, agglutination and complement fixation tests are all negative.

In penicillin hypersensitivity, Boget *et al* (2) point out the interesting fact that there seem to be no specific rules, and both immediate and delayed reactions may occur. As an example, they discuss the case of a 58 year-old bronchial asthmatic patient (17 years duration) who developed a respiratory infection for which he was given 400,000 units of procaine penicillin intramuscularly. He had had penicillin on a number of previous occasions with no reactions. Within a minute, he became flushed, dyspneic, developed marked asthma and urticarial wheals on the chest and abdomen. Eleven months later, he was given a skin test for penicillin G and O. The immediate tests were negative but there was a delayed positive reaction 48 hours later; a raised area, with induration, redness, and itchiness. Passive transfer antibodies could not be demonstrated in the blood. However, at this time, the patient acted as the recipient of blood from a patient being treated with penicillin and having

DRUG ALLERGY

a positive immediate skin test; he reacted at the site of injection by a wheal and erythema. Five months later, both penicillin G and O gave positive immediate reactions and no delayed reaction. The passive transfer tests were still negative.

Heggie (12) on the other hand obtained evidence of circulating antibodies being present, at least, shortly after the reaction. He presents the results of an experiment at the U. S. Naval Medical Research Unit where 62 persons showed allergic manifestations from benzathine penicillin prophylactically given to 16,000 men against streptococcal infection. The treatment was given because of a high incidence of acute rheumatic fever. Three groups were studied. In group I were men who about twelve days after an intramuscular injection of 1,200,000 units of benzathine penicillin had urticaria which, in some, was accompanied by arthralgia and joint swelling. Group II were men who had no sequelae to the same dose. Group III were men who did not get the prophylactic dose due to previous penicillin reaction. To test serum for circulating antibodies the method of Ley *et al* was used. (11) Human erythrocytes coated with penicillin were incubated, then washed with saline. They were used together with the patient's serum in a haemagglutination test. In group I, 29% showed antibodies, whereas in group II, 85% showed the presence of antibodies. In group III, 4.1% showed antibodies. This may indicate that antibodies formed in previous allergic episodes do not last for a long time. (12)

EXPOSURE.

Before considering the types of conditions produced, it is valuable to consider the effect of different portals of entry of a drug as related to the severity of the condition produced. When injected intramuscularly, hypersensitivity depends on the total dose, total time of absorption and the vehicle of the drug. Oily or lipid vehicles contribute to sensitization because they tend to evoke focal tissue reaction. It has also been observed, especially with penicillin and sulphonamides, that topical application for skin lesions leads to higher incidence of sensitization than if the drug is administered by mouth or injection. Experimentally, Sulzberger (1) treated artificially produced burns with sulpha ointment and sensitized the skin of 19% of 259 volunteers. Another interesting point brought out by Carr (1) is that dermatitis may often be produced when administration is not by skin route but by mouth, subcutaneously or intramuscularly; yet attempts to sensitize lab animals via the oral route have been unsuccessful.

In most cases the oral administration of drugs

seems to be the safest route. Even so, severe reactions may occur. Batson (6) points out that severe anaphylactoid reactions to oral penicillin have taken place on occasion. He reviewed 28 cases in recent English literature. The ages of the patients varied from 2-57 years, but only two were under 22 years old. Any number of the following immediate reactions was common: nausea, vomiting, facial edema, numbness or pruritus, cyanosis, respiratory distress, unconsciousness. Eighteen of the patients had severe hypotension. One patient had immediate symptoms followed several days later by serum sickness.

Although most sensitization occurs during therapy with a drug, it must be recognized that there are hidden sources of exposure. Nilsson and Sisson (3) emphasize such means of exposure to penicillin. (1) Transfer of sensitization may occur *in utero*. (2) A common antigen with penicillin has been found in the human mycosis, *Trichophyton*. Vesicular eruption after penicillin injection at a site of a long dormant tinea infection may be attributed to this common antigenicity. (8) (3) Inhalation or ingestion of spores from mould which may be related antigenically to mould producing penicillin may be a sensitizing source. (4) Penicillin is sometimes present in milk and dairy products when the cows have been treated for mastitis with penicillin. (5) Contaminated syringes may be the source. Nilsson points out that a solution of penicillin boiled for 16 hours still produced a positive passive transfer test reaction in a site previously sensitized. (6) Vaccines containing penicillin are now being discarded because of the serious reactions produced. (7) Penicillin dust in the atmosphere cannot be forgotten, especially in hospitals and manufacturing plants, where it is an added source of danger to sensitized personnel.

MANIFESTATIONS OF ALLERGY

Symptoms depend on many factors such as hereditary effect of localizing the reaction in certain organs, the frequency and means of exposure, allergic tendency with history of allergy to other causes than drugs.

Some of the reactions are similar to those of any foreign protein, polysaccharide or other complete antigen, i.e. asthma, conjunctivitis, serum sickness, polyarteritis nodosa. Some other manifestations are common only to drug allergies, i.e. drug fever, hepatitis, bone marrow depression. (1)

SERUM SICKNESS-LIKE REACTION.

1-2% of patients (2) receiving penicillin get a delayed illness after 5-14 days which varies from a brief urticaria of palms and feet to severe illness, often accompanied by arthralgia, lymphadenopathy, and fever up to 105°. The urticaria

may be massive and confluent. There may be edema of the face, especially around the eyes and hands. Various types of penicillin, crystalline and procaine, produce essentially the same incidence and severity of reaction. Penicillin in beeswax or oil produces an unusual rise in incidence of sensitivity.

DERMATITIS

A macular or papular rash may be produced with penicillin, phenobarbital, or sulphonamides. In penicillin therapy, if the rash is mild, treatment may be continued in spite of the reaction. (2) Often however, it progresses to an exfoliative dermatitis which may remain a problem long after drug therapy is discontinued.

DRUG FEVER.

Harrison (14) lists 36 drugs which are known to cause fever. This symptom may be unaccompanied by other manifestations, the temperature occurring suddenly just after initiation of therapy, or it may progressively rise in stages during or after the second week of therapy. It then may take several days for fever to drop to normal after the drug is withdrawn. (1)

DEPRESSION OF BONE MARROW

Allergic basis for marrow depression is questioned by Harrison. Carr, (1) however, presents an extensive chart of drugs producing agranulocytosis, thrombocytopenic purpura, and aplastic anemia.

DIFFERENTIAL DIAGNOSIS

In discussing the mechanisms of allergic reactions it was pointed out that although circulating antibodies may be present, often precipitin, agglutination, complement fixation and passive transfer tests are unreliable. Clinically, it is often difficult to differentiate the symptoms and signs of drug allergy from other conditions. For example, after an injury, both anti-tetanus toxin and penicillin may be prophylactically given. If serum sickness-like reaction occurs it is difficult to establish which is the cause. Administration of penicillinase is not worthwhile as a differentiating measure since it is only effective in 50% of cases. (9)

Gotsis and Harris (4) note that the cardinal symptoms of acute rheumatic fever and penicillin serum sickness are very similar, that is, fever, arthralgia, swollen, red painful joints, and skin eruptions. However, the rash of serum sickness is more frequently urticarial while in rheumatic fever, erythema multiforme is more common. Fingers and toes may be swollen in serum sickness, but much less frequently in rheumatic fever. Cardiac murmurs, on the other hand, are more common in rheumatic fever. A falling antistrept-

tolysin titre suggests serum sickness rather than rheumatic fever. Symptoms in serum sickness usually do not respond to salicylates but are often relieved by corticosteroids.

SAFETY MEASURES

Almost all the articles reviewed stress, very strongly, the importance of careful scrutiny in using certain drugs, especially penicillin and serum, and the importance of careful technique of administration. A careful history of allergic reactions must be obtained to the particular drug in question, to other drugs, and to any other substance. Even though the history is negative, Nilsson (3) points out that the chance of preventing rheumatic fever, acute glomerulonephritis or otitis media following a sore throat with fever is 0.42% while the chance of incurring a penicillin reaction is 2.5% in children, 5% in non-allergic adults, and 15% in an allergic person. Subacute bacterial endocarditis due to penicillin susceptible haemolytic streptococcus (diagnosed by culture and sensitivity) is one of the few remaining indications for its use prophylactically. The chances of harm outweigh the advantages of preventive use of penicillin for undefined infection. When administering by intramuscular or subcutaneous method, a drug, which is known to be antigenic, should be injected in the arm or leg so that a tourniquet may be applied should symptoms of anaphylaxis occur. Great care should be taken not to administer the dose intravenously by accident. Another precaution is to inject one or two drops, then wait 10-20 seconds before injecting the rest, watching carefully for any anaphylactoid reaction during that time. Vials of epinephrine, Levophed, aminophylline, cortisone, and antihistamine, as well as oxygen and a tracheotomy set should be available for symptomatic treatment of reactions. (7)

Skin tests are a help in detecting sensitivity, but in a highly sensitive person the test itself may produce a serious reaction. For testing penicillin sensitivity, a drop of penicillin G (5000 units/c.c.) is placed on the skin which is then scratched through the drop. If no reaction occurs, this is followed by 0.02 ml of penicillin G (1000 units/c.c.) intradermally. (7)

CONCLUSION

"Drugs have usurped the role once ascribed by Osler to syphilis, of being 'The Great Imitator'". (7) Allergic reactions to drugs certainly present a variety of signs and symptoms, can be prevented with care, and can be treated promptly by a physician who has a good knowledge of drug hypersensitivity.

DRUG ALLERGY

BIBLIOGRAPHY:

1. Carr, E.A.; New. Eng. J. Med.; 245:892, 1951.
2. Boger, W.P., Sherman, W.B., Schiller, T.W., Siegal, S. and Rose, B.; J. Allergy; 24:383, 1953.
3. Nilsson, D.C. and Sisson, J.C.; Postgrad. Med. J.; 27: 4-11, Jan. 1960.
4. Gotsis, C.A. and Harris, L.; New York State J. Med.; 59:3834-6, Oct. 15, 1959.
5. Arberman, C.E. *et al*; J. Allergy; 31:257-72 May-June 1960.
6. Batson.; New. Eng. J. Med.; 262:590-5, Mar. 24, 1960.
7. Current Therapy, 1960.
8. Cormia, C.F. and Lewis, G.M.; J. Invest, Derm.; 7:375. Dec. 1945.
9. Friedlanders, S.; J. Allergy; 30:181, 1959.
10. Logue, J. T. and Barrett, J. T.; Postgrad. Med.; 6:672-4 Nov. 1959.
11. Ley, A.B. *et al*; Science; 127:1118, 1958.
12. Heggie, A.D.; New. Eng. J. Med.; 262:1160-3, June 9, 1960.
13. Boyd, W.C.; Fundamentals of Immunology p. 382 Interscience Publ. Inc. N.Y. 1956.
14. Harrison; Principles of Internal Medicine.
15. Rapoor, O.P. and Sathe, R.V.; J. Indian Med. Ass.; 34: 57-8. Jan. 16, 1960.

TREATMENT OF CHORIOCARCINOMA WITH A COMBINATION OF CYTOTOXIC DRUGS:

K.D. Bagshawe, and J.M. McDonald: British Medical Journal, Aug., 1960.

As a result of the work of Hertz and Li (1956), some success has been achieved in the treatment of malignant trophoblastic tumours with folic acid antagonists. However, in many patients after an initial remission the tumour subsequently became resistant to the agent used. This paper describes an attempt to prevent the development of drug resistance by means of a combination of cytotoxic agents.

The agents used were methotrexate (a folic acid antagonist) and 6-mercaptopurine (an adenine antagonist). If there appeared to be any signs of developing resistance then Chlorambucil would be substituted for 6-mercaptopurine.

Six cases, all with proven choriocarcinoma and all with multiple metastases, are presented. Some of the patients had received prior surgery or radiation. The drugs were given in massive doses in staggered 3-5 day courses, and under antibiotic cover. Patients were followed by white counts and gonadotrophin excretion titres. In some of the patients, bone marrow was removed and stored against possible irreversible marrow depression. It was not found necessary to make use of it, however. Treatment was continued till the urinary gonadotrophin titres had been within normal limits for 6-10 weeks.

Toxic side effects such as stomatitis, nausea, alopecia, and bone marrow depression were noted. One patient died during treatment. Autopsy revealed extensive renal infection and hepatocellular damage. All tumour tissue was necrotic. The other five patients achieved complete clinical, radiological, and hormonal remission. At the time of reporting the duration of remissions has ranged from 2-19 months.

TREATMENT OF MULTIPLE SCLEROSIS WITH TOLBUTAMIDE

G.T. Sawyer: The Journal of the American Medical Association, Oct. 1, 1960.

A preliminary report of the treatment of seven patients with multiple sclerosis with tolbutamide was alternated with placebo in six of seven patients. In addition, the dietary CHO was changed between high and low values. In all cases, the administration of tolbutamide except when combined with a high CHO diet was followed by remission of symptoms. Likewise, every instance of placebo substitution was followed by exacerbation. It was generally felt that a low CHO diet was beneficial and that a high CHO diet was detrimental. The author goes on to discuss briefly the theories concerning the relationship between multiple sclerosis and abnormalities of carbohydrate metabolism. A further, more extensive study of the value of tolbutamide therapy is planned.

THE CLINICAL EXPRESSION OF MAGNESIUM DEFICIENCY

W.O. Smith *et al*: Journal of the American Medical Association, Sept. 3, 1960.

The clinical picture of magnesium deficiency is principally characterized by neuromuscular and CNS hyperirritability. A tremor consisting of choreiform or athetoid movements is seen in most patients. Marked sudden irregular jerks and aimless plucking at bedclothes has been observed. The tremor, at times, may resemble a liver flap. Clonic convulsive seizures have been noted. Mental aberrations observed include disorientation, confusion, and finally true hallucinations. Reflexes are generally hyperactive.

In pure magnesium deficiency, the signs of true tetany are not seen. Causes of magnesium deficiency include prolonged intestinal obstruction, prolonged diarrhoea, excessive diuresis, and osteolytic metastatic lesions.

CUTANEOUS MANIFESTATIONS OF DRUG REACTIONS

W. A. YORZYK, M.A., 6T1.

INTRODUCTION

Quite often in the treatment of disease, it is found that a serious therapeutic complication is the unanticipated and unelicited, reaction to the medication being used. Due to the manner in which these reactions occur, it is logical to assume that they are a manifestation of allergy. A simple definition of drug allergy is that it is a sensitivity to medicinal agents, of one type or another. The drugs, as allergens, bear no relationship to each other, except that they are all used as remedial agents. If a drug allergy exists, manifestations of this allergy will occur in almost every tissue and organ in the body; however, this discussion will be primarily concerned with the cutaneous eruptions. *Dermatitis medicamentosa*, or drug eruption, should not include true contact dermatitis, and is used solely to refer to the rashes produced by the adsorption of some drug. This adsorption may occur in many different ways—not only by injection or oral administration, but also by inunction, inhalation, enema, through vaginal epithelium, through mother's milk, etc. There are few, if any, drugs which have not evoked an eruption at one time or another and the list is continually growing. However, some drugs are more liable to produce reactions than others, and our main concern will be with these. A special section will be included on the allergic reactions to the tranquilizing drugs, as these preparations are being used with more and more frequency.

MECHANISM

It is not possible to state with certainty, the pathogenesis of all the drug reactions; however, certain reasonable hypotheses may be advanced. Among the more important mechanisms are (1) enzymatic interference, (2) allergic sensitization, (3) a Schwartzman reaction, (4) a Herxheimer reaction, and (5) ecological interference. (18) It is an oversimplification to state that a patient is allergic to a drug merely because some sort of reaction develops while he is taking it. An investigation into the specific mechanism of the reaction is important to the patient, because it governs the advisability of continuance of the drug in question.

ENZYMATIC INTERFERENCE

Many drugs achieve their therapeutic objective by interference, usually competitive, with some enzyme system, either in the host or in the invading organism. According to many authorities, side-reactions of some drugs are the unexpected

consequence of a enzymatic interference (22). Motulsky (13) has suggested that a possible explanation for some drug reactions may be that the persons in whom they develop are biochemical deviants. Under ordinary conditions this deviation does not produce overt manifestations but under conditions of stress, as in the exposure to a particular drug, the result is different. He also suggests that some of the reactions that have been labeled idiosyncratic may be examples of biochemical deviation. At one time the fact that the liver, kidneys and lymph glands were involved in drug eruptions appeared to indicate that interference with the reticuloendothelial system might be responsible. Many authorities (14) believed that the production of antibody was not a function of a cell type but a complex activity of more than one form of cell, taking place in situations where phagocytic cells of the reticuloendothelial system are associated with lymphocytes and undifferentiated mesenchymal cells. However, there is, now, experimental evidence (14) that the production of these antibodies occurs in the skin, fat, voluntary muscle, and cornea, and not in the liver, spleen, or bone marrow. Peters *et al.* (15) lent considerable support to the "enzyme theory" when they showed that the partial blocking (or partial deficiency) of an enzyme system can cause pathological changes in tissue. Some recent experimental work (14) indicates that the complex cellular system of enzymes and co-factors is associated mainly with the mitochondria; suspensions of washed mitochondria can catalyze all the events which compose its actions. These particles can be disintegrated to some extent. It may be proven in the future, that the interference is specifically with the molecular linkage of DNA. It has been demonstrated that arsenic and other heavy metals can be liberated from cells by the administration of BAL (15), so that they no longer interfere with enzyme action. These drugs can produce many different types of rash in the same person (as in the severe bullous reactions to barbiturates and the closely related hydantoin compounds). It is logical to assume that the mechanism by which this occurs is enzymatic interference with the DNA molecule.

ALLERGIC SENSITIZATION

It has already been stated that it is an error to assert that a patient is allergic to a drug merely because some sort of reaction develops after he takes it. However, some drug reactions are brought about because of allergic sensitization, but, this does not mean that a circulating antibody will necessarily be demonstrable. (19)

CUTANEOUS MANIFESTATIONS OF DRUG REACTIONS

SHWARTZMAN REACTION.

This is a hemorrhagic, necrotic reaction brought about by a bacterial product which makes the treated tissue more sensitive to proteolytic enzymes. The subsequent administration of a drug (eliciting factor), by lowering the titer of proteolytic enzyme inhibitors and causing the formation of leukocytic platelet clumps, produces extensive damage. It has been shown that the union of an antigen with its antibody produces the same effects as the Shwartzman eliciting factor. It is evident then, that such a mechanism is a serious menace in any infection for which the patient received a drug to which he may be sensitive. Purpura and cutaneous ulcerations may result.

HERXHEIMER REACTION

This is a reaction caused by the wholesale slaughter of microorganisms with the consequent release of toxic or allergenic material, which in turn can produce reactions by any of the previously mentioned mechanisms.

ECOLOGIC INTERFERENCE.

The balance existing between tissue cells and certain microorganisms, which, under ordinary conditions, is stable, can be easily upset by drug administration.

A very interesting report which may throw some light on the mechanism of drug and other allergies, is that of McIntyre *et al.* (11) He describes the release of histamine from rabbit blood by two types of simple molecules — the long-chain aliphatic primary amines and the quaternary pyrimidine esters with large aliphatic groups attached to the nitrogen atom. His work, may be summarized as follows:

- (1) it is apparent that histamine is present in some bound form in the various tissues.
- (2) it may be released by simple chemicals whose molecule is very small as compared with antigens.
- (3) closely related compounds may not only fail to release histamine, but actually may inhibit the action of these releasing agents.
- (4) the mechanism is probably explained by some modification of the "receptor concept".
- (5) the reactions may occur without the necessity of antibody action.

It is apparent, after reading through these varied hypotheses of drug eruption mechanisms, that considerable confusion exists. However, the most widely accepted feeling at the present time is that these reactions are a result of antigen-antibody formation. Using this thought as the basis of explanation of drug reactions, one might be hard put, however, to include reactions to

drugs such as iodides, flourides, etc. These drugs are not antigenic in character, for when applied topically, no allergic manifestation occurs. Yet, when ingested and in the blood stream, most certainly, drug eruptions appear in many patients. There are numerous documented accounts of this in the literature. A possible explanation might be that the non-antigenic molecule, and thereby gains its antigenicity.

In 1940, Sulzberger (22), a well recognized authority in the field, set forth certain criteria for drug eruptions due to a drug allergy. These have been accepted as valid and accurate criteria, and are still used by present-day dermatologists. These criteria are:

1. Very minute amounts of a drug which has been well tolerated for weeks, months, or years, may suddenly produce severe eruptions.
2. Once an eruption has occurred it may recur upon subsequent minute exposures to the offending or a related drug.
3. As a rule, the cutaneous response is entirely different from that produced by the pharmacologic or toxic action of the drug.
4. Drugs with entirely different pharmacologic actions may produce identical eruptions. The same drug may produce different manifestations in different persons, or in the same person at different times.
5. The amount required to elicit eruption may be much smaller than that required to produce pharmacologic or toxic effects.
6. Many drug eruptions occur only in predisposed persons and cannot be made to appear in the majority of individuals.
7. The role of cumulative effect can be ruled out. Eruptions can recur upon re-exposure to small amounts even years after the last exposure.
8. Marked specificity of drug sensitivity can often be demonstrated. Group specificity and cross reactions may be demonstrable.
9. The usual forms and phenomena found in other allergic conditions are duplicated by the drug eruptions.
10. Many substances which produce drug eruptions also may sensitize the skin of human beings and of laboratory animals."

MORPHOLOGY

The term, dermatitis medicamentosa, connotes a more or less generalized symmetrical, slightly bizarre eruption; however, drug eruptions can mimic the appearance of any of the dermatoses. (18) The more common morphologic varieties of drug eruptions are (1) erythematous or exanthematous, or both, (2) eczematous, (3) urticarial, (4) erythema multiforme like, (5)

acneiform, (6) lichenoid and (7) fixed — (18). Certain drugs tend to produce a particular morphologic response, but this is only generally true, and probably any drug can occasionally cause any type of cutaneous lesion.

An *erythematous* or *exanthematous* drug eruption is one in which the basic component is an erythema, on which other lesions such as papules or vesicles may be superimposed.

An *eczematous* drug eruption is one in which there are areas of closely aggregated papules and vesicles. Spongiosis is seen on section. This reaction is very much like the previous one, and the chief difference is that the patches of eczema tend to be discrete and, usually, the amount of cutaneous involvement is less. Arsphenamine, the sulfonamides, and the modern antituberculosis drugs are outstanding examples of substances which can produce this type of reaction.

An *urticarial* reaction is one that consists of wheals. The skin in between these wheals may or may not be erythematous. The lesions are more likely to present at pressure points.

Erythema multiforme presents as erythematous papules, and may be hemorrhagic. These papules have an area around them so that they resemble an iris, and hence called, "an iris lesion".

In *acneiform* eruptions, the essential lesion is the comedo, which may have a superimposed infection, with the formation of the typical acne pimple. However, in drug eruptions, the comedo is not often seen. What actually develops is an acneiform pustule, occurring in areas in which acne vulgaris is most often seen.

A *lichenoid* eruption is one in which tiny papules form, which tend to coalesce, and are dry.

The *fixed* reaction is one in which an erythematous macule becomes pigmented. The term "fixed" indicates that each time there is a reaction, the old sites flare, disappearing in the intervals between exposure. If exposures are repeated, the lesions may stay pigmented, and new ones may appear, so that eventually large parts of the body are covered.

DIAGNOSIS

As a rule, there is no difficulty in *suspecting* a drug eruption. Proof of the same is another matter. Diagnosis of a drug eruption depends primarily upon the alertness and suspicion of the attending physician. There are no pathognomonic signs by which one can diagnose a drug eruption with certainty. History is most important. Often a patient who is asked if he has taken any drugs recently will answer negatively, even though he may have taken laxatives, aspirin, Bromo-seltzer, etc., regularly. It is necessary for

the physician to enumerate each item, and go over each system methodically, remembering that drugs do not have to be ingested to cause reactions. A scalp lotion or a salve for *tinia pedis* may be the source of the trouble.

Skin tests do not seem to be of particular value in demonstrating the etiologic role of a given drug. The only evidence that establishes a causal connection is the cessation of the eruption when the drug is discontinued, and its appearance again when the drug is re-administered. However, it is important to rule out other forms of dermatitis by the usual investigation.

THERAPY

It is the duty of the physician to obtain an adequate history regarding adverse reaction to chemicals from the patient. Potent drugs should not be prescribed unless there is a definite indication for their use. If the risk of a severe reaction to a drug is great, but its use seems quite desirable, corticosteroids may be invaluable, (4) e.g., in a person gravely ill with tuberculosis and sensitized to streptomycin.

Rostenberg (19) has devised a scheme for drug-reaction therapy, described as "A, E, I, O, U," "A" stand for avoidance. "E" stands for elimination or eradication, which denotes using other drugs that will either expedite removal of the offending drug or destroy it. "I" stands for immunologic therapy, or desensitization. This is a most controversial point among most authors, and the general consensus is that it should be used only as a last resort and if substitution is not possible. "O" stands for obstructive therapy, or the use of measures that tend to block or antagonize the mechanisms by which the drug produces its reaction or to ameliorate or slow down the inflammatory consequence of the drug reaction. Finally, "U" stands for unguental, or usual topical therapy. The primary symptoms where this form of therapy is indicated are itching and burning. Colloid baths have some soothing and antipruritic qualities. Various "caine" derivatives may be used, although these may cause a dermatitis in themselves, as they are primary irritants, and as such, are to be recommended only with great care. It is important to remember that the inflamed skin is more vulnerable to the development of sensitization. Therefore, systemic sedatives or tranquilizers are often very useful.

The essential principle in drug-reaction therapy, is to use plenty of common sense. Not only the drug apparently responsible for the rash but also all other medicaments must be stopped if possible.

Patients with minor reaction can continue their normal mode of life and need only to stop taking the drug, but patients with more severe reac-

CUTANEOUS MANIFESTATIONS OF DRUG REACTIONS

tions require hospitalization, as skilled nursing care is of the utmost importance. (14) Antihistamines can be expected to relieve symptoms only in cases of rashes with an urticarial element and should not be given routinely. In general, vitamin therapy is disappointing, but may be helpful in isolated reactions. (14) Cortisone and related substances should not be used haphazardly, but only if there is good reason for prescribing them. (3,5,6) The steroids are indicated for any patient with severe toxic symptoms.

In local treatment of drug eruptions, the type of rash determines the form of local applications. They should be similar to those used for the disease imitated by the drug eruption. For exudative, vesicular or bullous conditions one can recommend compresses of Burrow's solution (24) diluted 1:10 with sterile water, or 0.5% eosin solution, with a spread dressing of petrolatum containing 12% zinc oxide on top. For erythematous and papular eruptions, shake lotions dabbed on several times daily are all that is needed, e.g., 2% ichthymol in calamine lotion or hydrocortisone or prednisolone can be combined with quinalone drugs. For exfoliative dermatitis, applications of dye such as 0.5% eosin or gentian violet covered with complete spread dressings of zinc past should suffice. In acneiform eruptions, 3% sulfur in calamine may be effective.

As a rule, tar preparations are not well tolerated by patients with drug rashes, especially if any element of photosensitization is present. In general, the mildest and most soothing treatments should be used rather than those liable to cause further irritation.

CUTANEOUS AND SYSTEMIC REACTIONS TO THE TRANQUILIZING DRUGS.

Tranquilizing drugs, like most drugs, may act as allergens. So many of them are appearing on the market that it is impossible to list them individually. Therefore, I have separated them into three rather general class. These are:

- (1) phenothiazine derivatives — especially chlorpromazine
- (2) rauwolfia alkaloids — especially Reserpine
- (3) substituted propanediols or butanediols — especially Meproamate.

Most of the allergic complications which occur with the use of the tranquilizing drugs are seen in the phenothiazine group, and the substituted propanediols. A few reactions have been reported in the literature for the rauwolfia alkaloids; however, these are rare and almost negligible.

COMPLICATIONS WITH PHENOTHIAZINE DRIVATIVES:

There are three general types of reactions to the use of these drugs. The drugs which most

often cause them are chlorpromazine, Promazine, Meprazine, Trifluopromazine, Prochlorperazine, and Perphenazine. By far the most severe complication with these drugs is agranulocytosis, even though it is rare. (25) An immunologic origin for this has been suggested by some writers, but as yet this has no experimental basis. Jaundice is a more frequent complication of these drugs. Its prevalence is quite high, being 1-3% of all patients treated for one week or more. It is of the intrahepatic obstructive type. (20) The following is a summary of the data concerning the clinical and laboratory characteristics of jaundice due to chlorpromazine: (7)

A. Possible precipitating factors:

1. older patients affected more often
2. no sex predilection
3. no relation to previous liver damage
4. occasional past history of allergy of drug reaction
5. no relation to the daily dose of the drug.
6. 80 — 90% discovered in the first 4 weeks

B. Clinical features:

1. fever, G.I. upset, malaise
2. enlarged liver, with or without pruritis
3. patient feels better with the onset of the jaundice
4. pain in right upper quadrant of abdomen
5. self-limited course
6. little residual liver damage

C. Laboratory picture:

1. BSP retention, increased alkaline phosphatase preceeding the jaundice.
2. increased direct Vandenberg reaction
3. Bilirubinuria early; urobilinogenuria
4. transient increase of serum lipids
5. transient positive flocculation test
6. may or may not have eosinophilia

The third and possibly the most rapid complication of chlorpromazine therapy is that of a dermatitis. There are three main types of skin eruptions due to reaction to the chlorpromazine drug. (9)

1. Systemic manifestations

- a. generalized eruptions, described variously, as maculo-papular, urticarial, petechial, edematous, and/or bullous.
- b. analagous to jaundice in its onset 9th-37th day.
- c. the rash clears spontaneously with the withdrawal of the drug, and does

not return upon subsequent administration.

2. Contact dermatitis
 - a. occurs on the hands of the drug handlers (physicians and nurses)
 - b. patch test positive
3. Photosensitive dermatitis
 - a. affects the exposed area
 - b. resembles sunburn, with or without oedema, vesiculation and/or petechiae
 - c. drug must be ingested to produce the reaction.

COMPLICATIONS WITH RAUWOLFIA ALKALOIDS

There have been very few allergic reactions, reported in the literature, for this group of tranquilizing drugs; in fact, only one case of angio-neurotic edema has been published, and one case of photosensitive dermatitis, clearing slowly over a 3 month period. (1) In general, then, it can be said, that the use of drug in this group is quite safe from allergic reactions.

COMPLICATIONS WITH THE SUBSTITUTED PROPANEDIOLS.

Allergic reactions in this group of drugs occur with the most intensity and the most frequency with the use of Meprobamate. The most often-reported reaction is that of chills, fever, vascular collapse (the most alarming symptom), G.I. symptoms, and skin rashes. These usually follow within hours of the 1st or 2nd dose of this drug. (3) The rash is described as urticarial, petechial, morbilliform, or as simple erythema, and showing a predilection for the pelvic girdle, breast areas, axillae, and dependent parts. (21)

1. The mechanisms of drug eruptions are discussed under 5 headings: These are:
 - (1) enzymatic interference
 - (2) allergic sensitization
 - (3) a Schwartzman reaction
 - (4) a Herxheimer reaction
 - (5) ecological interference

It is suggested that while blocking of cellular enzyme systems plays a very important role, this is possibly only the mechanism through which an antigen-antibody response is manifested.

2. Drug eruptions are described morphologically, and a note has been added regarding the diagnosis of these eruptions. It is stressed that it is the duty of the physician to take a painstaking history regarding allergic sensitization to drugs.
3. Therapy of drug rashes is discussed under general principles, minor reactions, and local treatment.
4. A special section has been included, on the cutaneous and systemic reactions to the tranquilizing drugs. These are discussed under three classes — phenothiazine derivatives, rauwolfia alkaloids, and substituted propanediols or butanediols. Special attention is given to certain drugs in each class — chlorpromazine, Reserpine, and Meprobamate.

ACKNOWLEDGMENT

The writer wishes to express his thanks to Dr. Sellers, Prof. of Pharmacology at The University of Toronto, the Department of Dermatology, Mrs. J. Tomczak, Chief Lab Technician, Queensway General Hospital, and Professor Charles E. Silvia.

BIBLIOGRAPHY

1. Cahn, C.H., "Complication During Reserpine Therapy." *American Journal of Psychiatry*. 112:64 1955
2. Dameshek, W., and Rubio, R.: "Drug Reactions". *Correspondence*. J.A.M.A. 167:2117 1958
3. Friedman, H.T., and Marmelgut, W.L., "Adverse Reactions to Meprobamate." J.A.M.A. 162:628-630, 1956.
4. Fromer, J.L., "The Use and Abuse of Cortico-steroids in the Treatment of Skin Diseases." *Medical Clinics of North America*. 44:521-30 March, 1960
5. , "Dermatologic Allergy VI. Critique and Review of Recent Literature." *Annals of Allergy* 13:479-524 July 1959.
6. , "Dermatologic Allergy VI. Critique and Review of Recent Literature." *Annals of Allergy*. 18:292-337. March, 1960.
7. Hollister, L.E., "Allergic Reactions to Tranquilizing Drugs." *Annals of Internal Medicine*. 49:17 1958
8. Ingram, J.T., "Dermatological Problems of Adolescence." *Practitioner*. 184:308-315 March, 1960
9. Levan, N.E., "Chlorpromazine Dermatitis. Occupational — immunological Aspects." *New England Journal of Medicine*. 256:651 1957
10. Lorcinz, A.L., Malkinson, F.D., and Rothman, "Cutaneous Manifestations of Incipient Systemic Disease." *Medical Clinics of North America*. 44:249-74 Jan., 1960
11. McIntyre, F.C., Roth, L.W., Sproull, M.: "Histamine Release in Rabbit Blood by Simple Molecules, Inhibition and Reaction Rate Studies." *American Journal of Physiology*. 167:233 1951
12. Lerner, A.G., "Enzymes." in Rothman, S., *Physiology and Biochemistry of the Skin*. University of Chicago Press. Chicago, Ill., 1954 (pg. 566)
13. Motulsky, A.G., "Drug Reactions, Enzymes, and Biochemical Genetics." J.A.M.A. 165:835 Oct. 19, 1957
14. Peterkin, G.A.G., "Drug Eruptions; Their Causation and Treatment." *Postgraduate Medicine*. 25:2 1959
15. Peters, R.A., Stocken, L.A., and Thompson, R.H.S.: "British Anti-Lewisite." *Nature*. London 156:616 1945
16. Questions and Answers: "Penicillin Allergy" J.A.M.A. 170:890 1959
17. : "Penicillin Reactions" J.A.M.A. 170:891 1959.
18. Rosenberg, A., "Drug Reactions." *Postgraduate Medicine*. 24:263 1958
19. Rostenberg, A.: "Dermatitis Medicamentosa." in Conn: (editor) *Current Therapy*. W.B. Saunders Co., Philadelphia, Pa., 1957 (pp.417-19)
20. Rotstein, J., Frich, P.S., and Shiele, B.C.; "Agranulocytosis Associated with Chlorpromazine Therapy." *Archives of Internal Medicine*. 96:781 1955.
21. Stroud, G.M., "Brief Recording — Drug Eruptions due to Meprobamate." *New England Journal of Medicine*. 256:354 1957
22. Sulzberger, Marion B.; *Dermatologic Allergy*. Charles C. Thomas Co., Springfield, Ill. 1940
23. Vaughn, W.T.; *Practice of Allergy*. Chapter LXIII. The C.V. Mosby Co., St. Louis, Mo. 1954
24. Warren, F.O.: "Treatment of Allergic Response to Penicillin — A Preliminary Report." J.A.M.A. 167:708 1958
25. Yules, J.H., and Baber, H.: "Agranulocytosis During Chlorpromazine Therapy" *Bulletin of the Tufts New England Medical Center*. 1:224 1955

CIBA

PRESENTS

"ON INSPECTION"



Fig. 1 - This 29 year-old woman developed swelling of the eyelids and conjunctivitis with rigors and fever (103.9). Generalized muscular pain ensued, accompanied later by weakness of left arm and hand with irrationality and visual hallucinations. Eosinophilia -26%. What are the common causes of splinter hemorrhages? What is the diagnosis?



Fig. 2 - This is a typical facies! A 54 year old woman, she has had decreasing exercise tolerance for two years with swelling of the ankles and 6 months of paroxymal nocturnal dyspnea. Jugular venous pressure is elevated to 3 cm. above the level of the sternal angle. The heart is enlarged; there is a left pleural effusion. ECG showed low T waves. Think of some other complications and give a precaution of therapy.

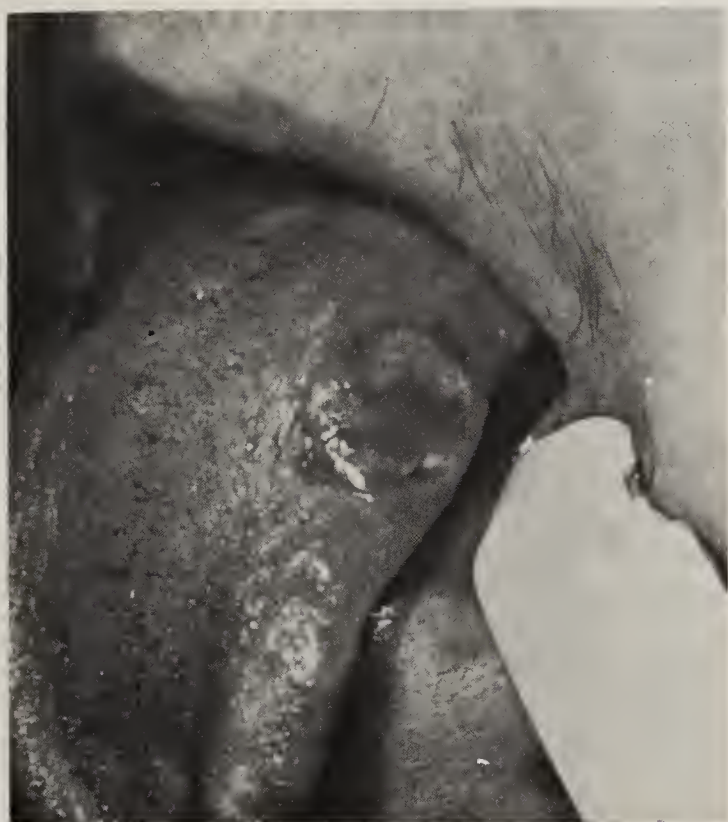


Fig. 3 - A common lesion, painless in its beginning, this should be an easy subject for a differential diagnosis, probable diagnosis and treatment.



Fig. 4 - The mucous membrane of the oropharynx is white, thick and smooth in the most anterior portion of the lesion. Further back, it is warty and fissured, and the middle area is ulcerated and necrotic. What is the diagnosis? Could there be malignant change?



Fig. 5 - What should a painful, bluish-red, indurated and swollen lesion consisting of multiple sinuses about the lower jaw or neck suggest? Pus from a sinus contained "cayenne-pepper" granules heavier than water. What is his probable occupation?

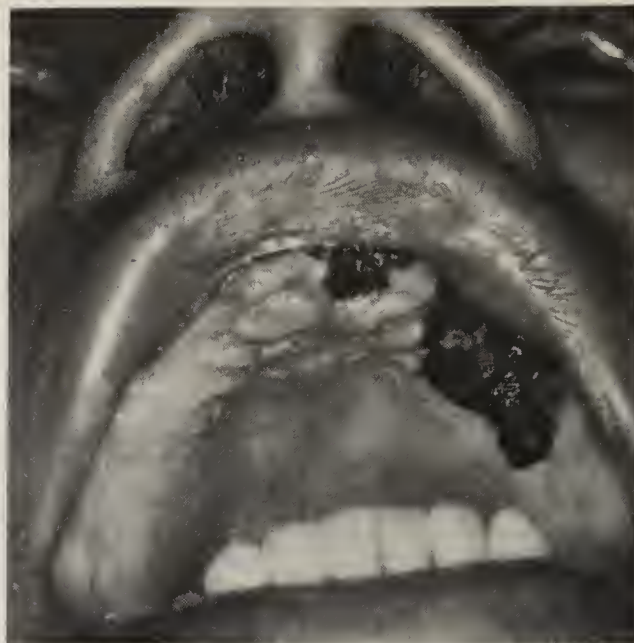


Fig. 6 - This is a black, rapidly spreading lesion. What is this lesion and from what does it arise? What changes in the latter would suggest treatment to prevent such development?

Answers to "ON INSPECTION" may be found on page 59.



Fig. 7 - What disease does this very characteristic appearance suggest to you? What other lesion may give a very similar picture?

L. M. JERRY, 6T1.
D. P. SMITH, 6T2.



Fig. 8 - What histologic picture would you expect to find from a biopsy of this lesion? What chances exist that distant metastases have occurred?



Fig. 9 - This lesion began as a pruritic papule and developed over several weeks into an umbilicated, pink and waxy nodule. What could it be? From what must it be differentiated?

AUTOIMMUNITY IN DISEASES OF UNKNOWN ETIOLOGY

WALTER SPITZER, 6T2.

The purpose of this paper is to show how recent experimental work in human blood serology has contributed to the understanding of the pathogenesis of a number of hematological diseases. This discussion will deal primarily with acquired hemolytic anemia (A.H.A.), idiopathic agranulocytosis, idiopathic thrombocytopenic purpura (I.T.P.), and disseminated lupus erythematosus (D.L.E.). There are parallels between the above conditions and better understood disorders such as hemolytic disease of the newborn. Comparisons will be made in the light of basic immunological principles. These principles will be stressed rather than details of the experimental work substantiating them.

INTRODUCTION

One of the most important body defense mechanisms is the ability of some of its tissues to synthesize antibodies that react specifically with foreign substances. These foreign substances may be a part of pathogenic viruses, bacteria or parasites. On the other hand they may be innocuous in themselves, as for example foreign serum proteins, erythrocytes or leukocytes. The body does not distinguish immunologically between the two types of antigens if they are foreign to the body.

There are different kinds of antigens and antibodies. Antigens vary immensely with respect to source, antigenicity, chemical nature and incidence in human antigen-antibody reactions. Antibodies are also classified in different groups according to several criteria. A complete classification is an extensive study in itself, but the types of antigens and antibodies relevant to this discussion are relatively few.

The antigens that blood serology is most concerned with are those found on the surface of red cells. These antigens are present in definite percentages of the human population. They are the basis of blood groups and the keystone of blood transfusion practice. Some substances found in the protoplasm of human leukocytes and platelets are able to stimulate the formation of specific antibodies against them in other humans.

Natural antibodies are synthesized in an individual in the absence of an antigenic stimulus. The anti-A present in a B group person is an example of this type.

Isoantibodies are those that are formed in an organism as a result of stimulation by an antigen foreign to it. The source of the antigen is another member of the same species. A good example of this is the anti-D which forms in a

D-negative (Rh-negative) person who is transfused with D-positive (Rh-positive) blood.

It is a maxim of immunology that the body is able to differentiate between foreign proteins and its own proteins. It has now been shown that under special circumstances a person's own tissues may stimulate antibody formation in that same individual. This process is referred to as autoimmunization and results in the production of autoantibodies.

Autoantibodies are subdivided in two groups according to their activity at different temperatures. The first group gives maximal agglutination or haemolysis at temperatures around 4°C. and the antibodies show a variable decrease in activity as the temperature is elevated to 37°C. These are called *cold autoantibodies*. If their thermal amplitude is wide enough their activity may persist at temperatures which the blood may reach in peripheral tissues such as the ears, nose and hands. *Warm autoantibodies* show good activity at body temperature. If they are present, they invariably cause damage. Cold antibodies may be present but inactive. However, the action of the cold type may be much more severe if the critical temperature for their activity is reached by the blood. Autoimmunization processes as manifested in disease often follow closely after infection, the development of some type of allergy, or similar conditions. One of the hypotheses to explain the occurrence of autoimmunization suggests that pathogenic agents in infective micro-organisms or chemical groups of drugs now used for therapy might cause constituents of the patient's tissues to become antigenic to him. The mechanism is not understood. One of the suggestions is that the substances introduced in the body act as haptens and give antigenic specificity to some body proteins, but this remains to be proved.

The classical studies in immunology have been made using antibody-antigen reactions in which the antigen is on the surface of the red cells and the antibody is in the plasma. This type of reaction has harmful consequences for the individual in which they occur. The mechanisms involved may not always be the same and are not perfectly understood. However, in the last fifty years both isoantibodies and autoantibodies have been ascribed an ever-increasing role in the production of disorders of the blood. This is particularly true with respect to the pathological destruction of various types of blood cells singly or in various combinations. Diseases affecting erythrocytes, leukocytes and platelets will be discussed in that order, showing how the concept of the pathogenesis of these diseases has evolved

AUTOIMMUNITY IN DISEASES OF UNKNOWN ETIOLOGY

as a result of improved serological techniques and new discoveries in this field.

ERYTHROCYTES

Acquired hemolytic anaemia due to isoantibodies has two forms: hemolytic disease of the newborn (H.D.N.) and hemolysis resulting from incompatible blood transfusion. In H.D.N., the hemolysis occurs in the newborn as a result of placental transfer of antibody from the mother to the child. The mother may form antibody when the foetus possesses blood group antigens which are different to her own. This phenomenon occurs if foetal erythrocytes are successful in crossing the placental barrier to the maternal side of the circulation. The antibody-antigen reaction in the circulation of the newborn takes place when the maternal antibodies attach to the surface of the erythrocytes. Similarly, in hemolytic transfusion reactions, isoantibodies in the plasma of the recipient coat the surface of incompatible transfused cells of the donor. Agglutination of the erythrocytes occurs in some cases but sometimes rapid hemolysis may lead to renal damage.

With these concepts in mind the role that autoantibodies have in the production of acquired hemolytic anaemia will be discussed. Dacie considers that the following variants can be produced by autoantibodies in the circulation of the diseased individual:

- (1) "Idiopathic" acquired hemolytic anemia.
- (2) hemolytic anemia following virus pneumonia.
- (3) paroxysmal cold hemaglobinuria.
- (4) hemolytic anemia associated with chronic lymphatic leukemia, reticulosarcoma, or disseminated lupus erythematosus.

In these conditions the patient is found to have formed antibodies against his own erythrocytes. It was thought for a long time that the antibody was specific to a substance found in all the cells of the individual. It is now considered that the antibody might be directed against blood group antigens found only on the surface of erythrocytes. Support for this theory was provided in a very convincing way by Weiner *et al* in 1953 (2). In serological studies of a man with A.H.A. and by use of antihuman globulin serum, they showed antibodies coating the surface of the patient's red cells. Then by eluting the antibody from the red cell, that is, by removing the attached antibody from the surface of the cell, they showed that the antibody had the blood group specificity anti-e. They went on to show that the patient's Rh genotype was CDe/CDe so that the patient had formed antibodies against an antigen found in his own body. The fact that the e antigen is present in 98% of white European population indicates how easily the anti-e found

in this patient might have been mistaken for a non-specific autoantibody.

In the hemolytic anemias associated with atypical pneumonia or paroxysmal cold hemoglobinuria (P.C.H.), the autoantibodies responsible are of the cold variety. The titre of the cold autoantibodies rises in these two conditions sometimes with more serious consequences than those observed in reactions involving warm antibodies.

A case report presented in 1954 by J. W. Harris (3), aids further in the understanding of how the hemolytic anemias may be produced. The report is brief and self-explanatory and is one of the few instances in which A.H.A. has been ascribed to a drug.

"An acute hemolytic episode developed in a twenty-four year old man, which was manifested by rapidly developing anemia, hemoglobinemia, methemoglobinemia, bilirubinemia, hemoglobinuria, reticulocytosis, spherocytosis, and increased erythrocyte osmotic and mechanical fragility; his erythrocytes gave a positive test in 1/2048 dilution of Coomb's serum. This hemolytic process occurred during re-treatment of schistosomiasis with Fuadin.

A factor was demonstrated in the serum of this patient that strongly agglutinated his own or normal erythrocytes; it was active only when Fuadin was present in the reacting system. Normal cells exposed to this serum became Coomb's positive, but only if Fuadin had been added. The agglutinin was non-dialyzable, not significantly influenced by pH or temperature alterations; it remained active in heated serum. Other antimony compounds and Catechol did not activate the agglutinin. However, the addition of sodium Catechol disulphamide potassium resulted in agglutination demonstrating that the entire Fuadin molecule was not necessary. Initially, the Fuadin requiring agglutinin was active in a 1/1024 dilution of the patient's serum but the titre gradually fell to 1/16 over a period of 60 days. Passive transfer of the agglutinin was effected by the administration of 300 ml. of the patient's plasma to a hematologically normal recipient. Five days after the plasma infusion, the recipient was given Fuadin intravenously. Although hemoglobinemia and bilirubinemia did not develop and the erythrocyte osmotic and mechanical fragilities were not significantly altered, gross erythrocyte agglutination did occur; the recipient's cells became Coomb's positive and the titre of circulating agglutinin diminished. It was present for a total of 26 days in detectable amounts." 3

Many of the hemolytic anemias which were previously classified as idiopathic can now be reclassified as autoimmune A.H.A. as further work in this field gives more proof of the existence of autoantibodies in these diseases.

LEUKOCYTES

Acquired agranulocytosis with an immune basis is now a well-known phenomenon and may be subdivided into three groups. The first group includes two uncommon conditions, neonatal isoimmune agranulocytosis and isoimmune granulocytopenia due to transfusion reaction. Because of difficulties involved in doing serological studies with leukocytes, it is uncertain at present whether the first of these is really a disease entity. However, destruction of transfused white cells due to an immune reaction in

which isoantibodies are in the plasma of the recipient has been observed frequently in blood transfusion practice. It produces rigor and transitory discomfort to the patient which can be prevented by removing the buffy coat from the blood bottle prior to transfusion. There is considerable evidence pointing to the possibility that agranulocytoses which have previously been classified as idiopathic are basically due to an autoimmune process.

Experimental evidence provided by Moeschlein (4) to show that immune agranulocytosis can be drug dependant is an important contribution in support of an immune basis of agranulocytosis. A summary of his experiments and their significance follows:

"In connection with a transfusion of 300 c.c. of blood from a Pyramidon sensitive patient (3 hours after 0.3 G. Pyramidon) there appeared within 20 to 40 minutes in two different recipients of the same blood group as the patient, an outspoken agranulocytopenia lasting from 3 to 5 hours. Controlled transfusions coupled with ingestion of Pyramidon produced no decrease in leukocyte number in these recipients.

In vitro, a substance was found in the plasma and serum of the patient at the height of Pyramidon agranulocytosis which produces agglutination of homologous and heterologous leukocytes. It is suggested that by this mechanism of agglutination, as for the erythrocytes in certain cases of acquired hemolytic anemia, the granulocytes are removed from the circulating blood and destroyed. The same mechanism may also be involved for a whole series of so-called anaphylactic agranulocytoses. An indication for this conclusion is found in another observation of ours of pancytopenia (hemolytic anemia, thrombocytopenia and granulocyte count of 230) in a patient with a high cold agglutinin titre (1/800) in association with virus pneumonia.

On the basis of these experimental findings, it is believed that the changes in the bone marrow are brought about by a precipitated depletion and exhaustion of the bone marrow due to the enormously increased peripheral destruction of the granulocytes rather than due to an actual inhibition of the marrow." (4)

PLATELETS

Certain cases of thrombocytopenia seem to be related to isoimmune phenomena. Similar to the development of agranulocytosis and hemolytic anemia mentioned above, neonatal thrombocytopenia occurs as a result of placental transfer of platelets from foetus to mother and antiplatelets from mother to foetus across the placenta. This has resulted in neonatal isoimmune thrombocytopenia. A decrease of transfused platelets has also been observed as one type of transfusion reaction in which antibody in the plasma of the recipient has caused a decrease in circulating platelets of the affected patient.

Recent work suggests that what has been called idiopathic thrombocytopenic purpura is also autoimmune in nature. In support of this, some workers have found positive Coomb's test and platelet agglutinins in patients with idiopathic thrombocytopenic purpura. (5) Other experiments proved that a platelet-destroying factor was present in these patients. A platelet agglutinin

was found in 50% of chronic patients and, in a majority of these patients, an *in vitro* test for platelet antibody was present.

Ackroyd in England has studied what he called allergic purpura in great detail. A summary of his conclusions follows: (1) All purpuras are primarily vascular lesions, and thrombocytopenia, if present, tends to aggravate the hemorrhages which occur. (2) The capillary endothelium and platelets seem to be antigenically related, so that an antibody which destroys one of these does the same to the other.

There are two types of allergic purpura; the Henoch-Schonlein syndrome and true allergic purpura. Purpura in the former is one of the manifestations of a generalized reaction which includes skin lesions and joint and visceral symptoms. It has been associated with hypersensitivity to foods but it has not been proved conclusively that this syndrome really has an allergic basis. The second type of purpura occur at the height of an infection with or without thrombocytopenia and its cause is an exaggerated susceptibility of the capillary endothelium to factors which operate normally in infections. As true allergic purpura occurs during convalescent periods, this phenomenon can be best explained at least in these cases, by assuming that an allergic process is directly responsible for the abnormalities present.

Purpura has also been shown to be drug induced in some cases. The drug responsible is Sedormid. Ackroyd believes that Sedormid acts by combining with the platelets, or the capillary endothelium or both, to form weak antigens. In other words, Sedormid has the properties of a hapten. Consequently, depending on the cells affected, this drug may cause uncomplicated thrombocytopenia, athrombocytopenic purpura or true thrombocytopenic purpura.

DISSEMINATED LUPUS ERYTHEMATOSUS

Patients suffering from D.L.E. usually develop anemia and this may be of the hemolytic type. It is believed that the hemolysis is sometimes due to autoimmune antibodies. The role of these antibodies in D.L.E. is not restricted to destruction of red cells for a similar phenomenon may involve the white cells; leukopenia is a common feature of the disease. There is an increase in the gamma globulin of the plasma in these patients and an interaction between their antibodies and leukocytes has been demonstrated. The main result of this interaction is considered to be the L.E. cell phenomenon, but destruction of the leukocytes themselves has not been ruled out as a possible mechanism. Miescher (6) believes that the L.E. cell phenomenon is caused by an autoimmune reaction. Thrombocytopenia may also

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occur in D.L.E. and the mechanism involved in the production of this manifestation is believed to be similar to that in anemia and leukopenia.

To conclude, and to illustrate the variety of diseases believed related to autoimmunization in their pathogenesis, some considerations of W. Dameshek and R. Schwartz (7) will be considered. These workers, associating autoimmunization and leukemia point out that immune reactions are known to stimulate the formation of certain leukocytic tissues. This leukocytic response occurs particularly in the reticulo-endothelial, lymphocytic and plasmocytic systems. Studies concentrating on the early phase of immune response reveal that the more primitive cells in these systems proliferate more than is normal and show a relative increase in mitotic figures. Accompanying these nuclear changes there is also an increase in the cytoplasmic nucleic acid and antibodies appear in the circulation plasma. High concentrations of antibodies in the circulation coincide precisely with the peak of proliferative activity observed cytologically and histochemically. In ordinary immune responses, the process above is self-limiting or temporary. However, a second equal antigenic stimulus elicits the immune response more readily. The immune process differs in this way from ordinary inflammatory or polymorphonuclear response to infections. Autoimmunization, in turn, differs from both in that once the stimulus provokes a response, the latter is not self-limiting and becomes permanent. Another difference is that the antibody formed is not directed to a foreign antigen, but to a constituent of the individual's own cells or tissues. The source of the antigen may or may not be found but it is undeniable that an antibody has been produced and

is demonstrable as a circulating gamma globulin.

With these facts in mind, Dameshek and Schwartz define autoimmunization as, "an abnormal, self-replicating proliferation of cells producing an abnormal protein, which is usually harmful to the host. As a continuous one, it is fundamentally different from the benign, reactive, self-limited type of immunological response." Dameshek and Schwartz then ask, "Does this therefore represent a formation of a new *race* of cells, genetically different, which continues to reproduce in an abnormal fashion and to produce abnormal protein?" If the answer to this is found to be in the affirmative their next question would be: "If . . . autoimmunization represents, at the cellular level, the proliferation of a new group of metabolically different antibody-producing leukocytes, does this not represent leukemic proliferation?"

The answers to these questions have not yet been given. However, an important new alley has been pointed out by Dameshek and Schwartz which may well lead to important conclusions about the etiology, pathogenesis and treatment of leukemia and other diseases with an autoimmune basis.

BIBLIOGRAPHY

1. Dacie, J.V., *The Hemolytic Anemias*. Grum and Stratton, New York, 1954.
2. Weiner, A.S. *et al*; *British Medical Journal*; II, 125, 1953.
3. Harris, J.W., *Journal of Laboratory and Clinical Medicine*; Vol. 44, p. 809, 1954.
4. Moeschlein, S. and Wagner, K.; *Acta Hemotologica*; Vol. 8, p. 29, 1952.
5. Evans, R.S.; *Archives of Internal Medicine*; Vol. 87, p. 48, 1951.
6. Miescher, P.J.; *Suisse Med.*; Vol. 83, p. 1042, 1953.
7. Dameshek, W. and Schwartz, R.S.; *Blood*; 14, 1151, 1959.

TISSUE TRANSPLANTATION AND THE HOMOGRAFT REACTION

P. C. SAMU, 6TI.

SCHEMA

Introduction.

The Homograft Reaction.

1. Fundamentals.
 - A. Antigenicity.
 - B. Successful Homografts Under Physiological Conditions.
 - C. First-Set Grafts (Primary Response).
 - D. Second-Set Grafts (Secondary, Accelerated Response).
 - E. Specificity.
2. Mechanism of the Homograft Reaction.
 - A. Role of Antibodies.
 - B. Role of Cells.
 - C. Nature of the Transplantation Antigen.
 - D. The Homograft Reaction as an Allergic Response.
3. Non-Specific Means of Weakening the Homograft Reaction.
 - A. Steroids, Irradiation, Dyes.
 - B. Agammaglobulinemia.
4. Specific Means of Weakening the Homograft Reaction.
 - A. Acquired Tolerance.
 - (i) Introduction.
 - (ii) Induction of Tolerance.
 - a) Adaptive Phase,
 - b) Neutral Period,
 - c) Mature Phase,
 - (iii) Mechanism of Acquired Tolerance
 - (iv) Special Types of Acquired Tolerance.
 - a) Maternally Induced Tolerance,
 - b) Tolerance to Malignant Cells,
 - c) Tolerance to Heterologous Antigens,
 - B. Immunological Paralysis.
 - C. Inhibition of Drug Allergy.
 - D. Phenomenon of Enhancement.
5. Clinical Application.

Summary.

INTRODUCTION

Tissue transplantation apart from being a fascinating subject, is one which in the not very distant future promises to be a practical one as well. One only has to glance at local traffic accident reports and synthesize them with his clinical experience to recall that for every fatality vividly described in the newspapers there is the lingering ghost of another fatality recorded in autopsy reports of patients dying because of a defective organ, such as heart, kidney or liver. They may have been saved if these organs from victims of violent death could have been transplanted. The potential importance of tissue transplantation speaks for itself and yet the medical student remains unexposed to the subject except through the most gymnastic of extra-curricular

shelf-scouting. In the following lines I shall attempt to atone partially for this shortcoming.

Hypothetically speaking, if one takes the horn of a mountain goat and implants it onto the forehead of a horse one does not get a unicorn, because the horn is rejected. This process or rejection is referred to as the heterograft reaction and is one of the most constant biological phenomena. On the other hand transplantation of tissue between members of the same species is possible after pre-treatment of the host (recipient of the transplant). No pre-treatment is necessary for transplanting tissue from one site to another in the same animal and such transplants are called autografts. From the three types of grafts mentioned the autograft presents no mysterious problems, the heterograft presents too many and the homograft, promising to be the most

TISSUE TRANSPLANTATION AND THE HOMOGRAFT REACTION

important from a clinical standpoint, is the one that shall be considered in detail.

Certain rules are found to apply to experimental transplantation of tissues in general.

1. Grafts are accepted among members of an inbred strain (one that is assumed to have an isogenetic constitution through prolonged and selective breeding).
2. Homografts are destroyed after an initial period of "take".
3. Offspring resulting from crossing two inbred strains will accept grafts from either parental strain.

These rules are the groundwork of experimentation in this line and dictate the design of planned experiments. For example, the fact that F1 hybrids (members of an inbred strain) accept each other's grafts allows the research worker to experiment on a statistical basis with a group of animals of an identical genetic constitution (for all practical purposes), instead of having to rely on individual animals with potential idiosyncrasies.

THE HOMOGRAFT REACTION (2)

1. FUNDAMENTALS

A. Antigenicity.

The antigenic individuality of tissue has been found to be governed by so-called histocompatibility genes. There are over seven such genes in the rabbit and it is estimated that in man at least twenty histocompatibility genes exist. From this assumption it has been calculated that there are at least one million antigenic combinations in the random human population, and that, if donor and recipient are chosen at random, about one in three hundred transplantations could be expected to succeed. Valiant attempts have been made to identify the genetic transplantation mates of individual patients. An apparent advance was the discovery that one of the most important genetic loci determining transplantation antigenicity was the same as the one that determined the type of hemagglutinogens contained in normal red blood cells. Consequently, it was hoped that red blood cell compatible individuals (transfusion compatible) would have a greater than one in three hundred chance of being graft compatible. Experimental juggling preceded these theoretical considerations and ample data are now available to indicate that blood typing in no way facilitates the selection of transplant compatible individuals.

B. Successful homografts under physiological conditions.

Homografts can be successful under the following naturally occurring conditions:

1. Close (or identical) accidental genetic similarity.
2. Mother to offspring grafts are assumed to be successful owing to cellular transfer of maternal cells into the developing fetus with the production of acquired tolerance (see Sect. 4A).
3. Between identical twins or members of inbred strains.
4. Fraternal cattle twins may accept each other's grafts as a result of mutual exchange of cells during fetal life resulting in acquired tolerance.

With the exception of the above physiological conditions transplants cannot be made to take permanently without pre-treatment of the recipient. It has been reported that endocrine organs such as the thyroid (17), adrenal (12), or ovary (10) sometimes survive as homotransplants in defiance of the rules, thus enjoying special immunological status. It is difficult to see why this should be so since the ovary contains stromal cells which do not seem to differ from connective tissue elsewhere in the body. Other workers (14) deny that this condition of immunological preference exists, and further investigation is needed. It should be noted, that grafts of bone and blood vessels widely used in surgery today, in no way defy the rules of homotransplantation. Such tissues are implanted as unobtrusively as possible to act as a scaffolding of more or less inert matter into which the recipient's cells infiltrate, or so it is hoped. These grafts are referred to as homostatic, whereas homovital grafts depend for their success upon the continued survival of the donor cells.

C. First-set Grafts.

(Primary response).

Studies of tissue changes have been extensively carried out on skin homografts. Immediately after the tissue is implanted there is a lag phase of five to six days during which no reaction is noted and the graft is indistinguishable from an autograft. The first one or two days of this phase are characterised by vascularization of the graft, and it has been shown that this is essential if subsequent rejection is to occur. It is suspected that more important than vascularization is the establishment of lymphatic channels, since it is known that regional lymph nodes play a significant role in homograft destruction. Thus, homografts implanted in brain tissue (which is deficient in lymphatics) survive for longer periods of time. If the transplant is made into the brain of a previously immunized animal the rate of rejection is as rapid as if it were implanted into any other tissue of the animal. Thus it seems that lymphatic drainage is important for the

process of ultimate graft destruction occurs independent of lymphatic drainage and, as evidence suggests, is mediated by the vascular supply. Following the first two days of vascularization and lymphatic permeation there follows a latent period of two or three days during which the immunological defences become geared for action.

On the fifth or sixth day definite histological changes are seen. The dermis is infiltrated with lymphocytes, immature plasma cells and eosinophils, the proportion of each varying with the animal species. This is followed by dilatation of the graft's blood vessels, with vascular congestion and eventual stoppage of circulation. The vascular endothelium as well as the epithelial cells are vacuolated, the nuclei distorted and these cells die together with the invading round cells of the host. The collagen elements become undermined by the host tissue, but occasionally the tissue grows over the graft's skeleton thereby producing unwarranted enthusiasm in the observer, who is apt to mistake this phenomenon for a "take".

The above sequence of events is referred to as the Primary Response and it characterizes the fate of homografts implanted into a host who had not been previously exposed to the donor's tissues.

PRIMARY RESPONSE

- I. Lag phase (5-6 days)
 - Vascularization (1-2 days)
 - Inactive phase (2-3 days)
- II. Reactive Phase (fifth or sixth day)
 - Cellular infiltration
 - Vascular degeneration
 - Sloughing (variable)

D. Second-set Grafts.

(Secondary, Accelerated Response.)

In reacting against a specific homograft the host loses its immunological virginity with respect to that donor. If a second graft is implanted after the first one has sloughed, the sequence of events differs markedly from the previously described primary response, and the graft is rejected with inimical brevity. This accelerated response is not confined to the region of primary grafting but extends through the whole body. The fact that the animal remains immune for very long periods of time (a lifetime for some species) indicates that the immunity is not due to the presence of any formed antibodies which might have been produced by the first reaction since the half life of gamma globulin is in the region of two days (in mice).

In the second-set graft, rejection proceeds so rapidly that there is no latent period. There is

no opportunity for vascularization or cellular infiltration to any extent, the brunt of the reaction being directed against the marginal tissues of the graft. It is difficult to account for the accelerated response. There is reason to believe that antigenic provocation never leaves the area of transplantation since the graft never becomes vascularized and it is unlikely that lymphatic channels could be established. Further, extirpation of the regional node (in the mouse) has no effect on the accelerated response, whereas it effectively delays the primary response. An alternate explanation presumes the presence of formed antibodies which is difficult to accept because, as was mentioned, the half-life of gamma globulin is in the order of two days. A favoured explanation argues by analogy that during the period of primary sensitization the cell population of the host had acquired a state of hypersensitivity in much the same way as the skin of a tuberculin sensitized animal demonstrates its sensitized state to local antigenic challenge.

E. Specificity.

The homograft reaction is individual or inbred-strain specific, but it has no tissue or organ specificity. That is, as far as the homograft reaction is concerned every organ of an individual possesses the same antigenicity. Thus, the secondary response to a graft may be obtained by previous sensitization with blood leucocytes, liver, spleen, kidney cell suspensions and, probably, other cell types. Red blood cells do not seem to have this power, though the matter is still controversial. Recent work demonstrating that transplantation antigens in normal cells reside in the nucleus and not the cytoplasm tends support those subscribing to the view that red blood cells do not possess the usual transplantation antigens.

2. MECHANISM OF THE HOMOGRAFT REACTION.

A. ROLE OF ANTIBODIES.

Because certain features of the homograft reaction would make it convenient to postulate the existence of circulating serum antibodies, many workers have attempted to identify such antibodies. However, in spite of careful *in vitro* and *in vivo* techniques, antibodies to homografts have proven consistently elusive. Thus, passive transfer of homograft immunity by means of "immune" sera has not been accomplished. On the other hand, heterografts do elicit formation of circulating antibodies which may be shown to be cytotoxic, although this does not prove that they are actually responsible for the heterograft rejection.

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B. ROLE OF CELLS

Recently, a line of interesting experiments has been designed utilizing porous membranes whose pores were small enough to prevent passage of cells but sufficiently large to allow free passage of gamma globulins. Imbedded as shown in the diagram (Fig. 1) they enabled homografts in mice to far exceed their expected survival time.

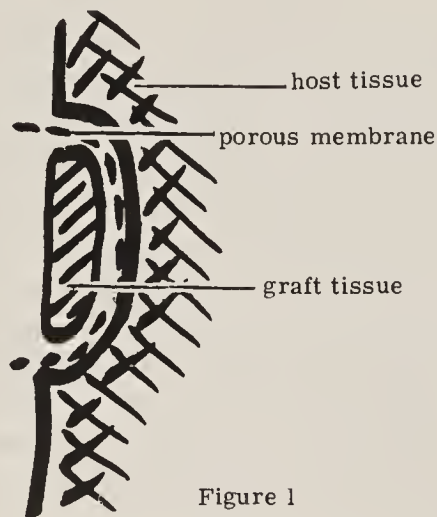


Figure 1

This was seen to hold true even for previously immunized animals. However, mouse tissue grafted by this technique into the rat did not prevent the usual heterograft reaction. This implies that cellular elements are not necessary for heterograft destruction while they do exercise at least some influence on the destruction of homografts. A curious sideline, which one expects would be extensively explored, is a demonstration that, in at least one type of malignancy (mouse leukemia), cytotoxic, circulating antibodies were present in the serum. (19) The less informed optimist prompted by this idea would attempt curing malignant disease with immune sera obtained by immunizing experimental animals with cancer cells. However, such a cure was attempted over half a century ago and unfortunately, the method has remained disappointing. (19)*

* If I may here interject some less informed optimism of my own, it might be interesting to see what would happen if the cancer cells were used to immunize animals that have previously been made tolerant to the patient's normal tissues (see section on acquired tolerance). The implication is, that if malignant tissue shares a considerable proportion of its antigenicity with normal tissue but in addition has a trace of individual antigenicity of its own, antibodies (if any) produced against the malignant cell in the patient might be absorbed and inactivated by the preponderance of normal tissue before they had the opportunity to act against malignant cells. Therefore, if malignant cells had a specific antigenicity it could be displayed in flying colours by the immunological response of the animal tolerant to normal cells. A non-specific immune response affecting normal as well as malignant cells in patients suffering from cancer would further explain the obscure cachexia associated with the disease, which would place this type of cachexia on a similar basis (and with almost equal justification) to the other auto-immune diseases.

There is now mounting evidence that circulating cells play an important role in the normal homograft reaction, while it is not yet known whether antibodies mediate the cellular action. They could do this either by transporting within themselves or on their surface preformed antibodies manufactured in the body's central immunological factory, or, alternatively, manufacturing antibodies peripherally, at the site of action. It has been shown that a primary response to a homograft can be elicited between members of an inbred mouse strain by transferring into the recipient lymphoid tissue from the draining lymph nodes of an unrelated mouse undergoing primary homograft response. (Contralateral lymph nodes, spleen cells, serum or blood leucocytes were ineffective.) Similar results were obtained when regional lymph node tissue was transferred into mice previously made tolerant to the donor tissue. This passive transfer of the homograft response was a singular advance in the field, and places the homograft reaction on a very positive foothold in the emporium of immunological phenomena.

Attempting to sum up the above and other evidence, it may be said that regional lymphoid tissue (and, to a lesser extent, spleen) becomes activated by homograft antigens leading to the production of immunologically potent cells or cell-bound antibodies. On the other hand, an additional process seems to be at work which induces a widely distributed peripheral sensitivity to subsequent grafting, since excision of regional nodes in the immune animal does not delay the accelerated response. It has been shown, also, that cellular infiltration into a graft is not a necessary prerequisite for a successful heterograft reaction, which may therefore be mediated by circulating antibodies.

C. NATURE OF THE

TRANSPLANTATION ANTIGEN.

Localization and isolation of the antigenic focus of tissue transplantation would enable the production of an immunological response by implantation of much smaller quantities of the antigenic concentrate than is required of the whole-tissue preparation. Such an increase in potency would serve as an index that the isolated material was, in fact, pure antigen or at any rate a step closer to the ultimate isolation. However, far from isolating pure antigen, until recently, all attempts at separation involving cellular disintegration resulted in loss of the ability of tissue to immunize. It had been, therefore, assumed that the living cell, structurally intact, was a *sine qua non* for its possessing antigenicity. Recent experiments, however, show that it may have been the method of cell disruption

rather than the principle of requiring whole cells which was responsible for loss of the immunizing capacity. It has been discovered that transplantation antigens are extremely unstable, their instability paralleling that of living cells, which makes it understandable that procedures short of the most elegant techniques (a fashionable phrase in research) destroyed antigenicity concurrently with the life of the cells. It is now pretty well accepted that the antigenicity of tissue with regards to transplantation immunity, resides in the nuclear portion of the cell, and nuclear extracts prepared by less traumatic methods have been effectively used in immunization with the result that subsequent attempts at homografting with donor's whole tissue met with a typical accelerated response. Unfortunately, it must be admitted that those nuclear extracts used for the immunizing exposure had to be used in greater quantities than would have been required of intact cell preparations. This, however, may mean nothing more than that in the process of isolation a large proportion of the antigen became inactivated, since it is known that the most carefully prepared *cytoplasmic* preparations, in however great quantities, are incapable of immunizing against subsequent transplantation.

Since it is known that histocompatibility genes are responsible for passing on the genetic individuality of tissue, attempts have been made to incriminate the DNA fraction of the nucleus in the actual eliciting of the homograft response. Were the incrimination justified, this finding would be illuminating as to the basic antigenic mechanism of the homograft response. Most recent work, however, has tended to absolve the DNA fraction.

D. THE HOMOGRAFT REACTION AS AN ALLERGIC RESPONSE.

For many years workers have attempted to draw an analogy between the homograft response and Arthus' phenomenon. Although a histological similarity exists, the analogy is being abandoned in view of the fact that circulating antibodies are not detectable in the homograft reaction. On the other hand, there seems to be increasing justification in regarding the homograft response and hypersensitivity of the delayed (tuberculin, bacterial) type as closely adjacent wave lengths on the immunological spectrum. The following points of resemblance may be cited:

1. Both reactions begin in 24 to 48 hours and persist for several days.
2. Both reactions are characterised by infiltration with round cells, especially lymphocytes and plasma cells.
3. Circulating antibodies are not detectable.

4. Passive transfer of both reactions is possible by means of viable cells from draining lymph nodes. It must be mentioned, however, that while multiple attempts at passively transferring homograft immunity by circulating leucocytes were consistently ineffective, delayed hypersensitivity can be easily transferred by leucocytes, even fractionated leucocytes.
5. Both reactions are weakened by administration of cortisone but not of antihistamines.

Unfortunately, certain inconsistencies have the effect of dulling the brilliance of this analogy. Thus, the delayed type of hypersensitive response can be transiently weakened by total body irradiation while this effect is not demonstrable in the *secondary* graft response. Also there seem to be certain differences in the types and proportions of the infiltrating host cells in the reactive area. On the whole, however, these objections are generally considered minor, and the modern immunologist tends to regard the two reactions as analogous phenomena.

3. NON-SPECIFIC MEANS OF WEAKENING THE HOMOGRAFT REACTION.

A. STEROIDS, IRRADIATION, DYES.

Much effort and grant money has been invested in the investigation of methods designed to weaken the homograft reaction. A number of substances was found to decrease the violence of the homograft reaction in a non-specific way (with respect to any antigen), and a quantitative estimation of the substances' potency may be derived by noting the prolongation of expected graft survival time. Thus, as would be expected, injection of hormones such as ACTH and cortisone, or their local application, were found to prolong somewhat tepidly the expected graft-survival time, their effect being variable in different species, but least potent in man.* The effect of these hormones on second-set grafts was almost nil in all species tested. Progesterone, testosterone and estrogen were found to have no effect, though it is known that the pregnant rabbit at a certain stage of gestation will tolerate a homograft for twice its expected survival time. (11)

Another means of non-specifically prolonging the survival of homografts is through total body irradiation of the recipient. In large enough

* This is not surprising since there appears to exist a correlation between the status of a species on the phylogenetic scale and the exquisiteness of its immunological responses.

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doses, this may even produce total acceptance by inducing a total failure of the central immunological mechanism. It is interesting to find that total body irradiation has no demonstrable effect on the fate of second-set grafts, which is pleasingly compatible with the suggestion expressed above that the accelerated response was possibly due to a peripheral state of tissue excitation as opposed to the primary response which involved the necessity of a central immunological indoctrination as evidenced by the occurrence of a latent period and the demonstration of the role played by draining lymph nodes.

An unexpected and probably not very illuminating finding is the ability of certain dyes, such as Trypan Blue, to produce prolongation of graft survival time. The effect is generally considered as being due to interference with the metabolism of antibody producing cells, many of them being known to take up the dye selectively.

The discovery that total body irradiation in large doses enabled permanent 'take' of homografts paved the way for another important discovery. Adult mice were irradiated with lethal doses of X-ray and instead of attempting to graft them with conventional tissue they were injected with the hemopoietic tissue of a genetically unrelated mouse. (15) This hemopoietic graft was not only accepted (as would be expected from the above) but in addition the graft served to protect the recipient against the otherwise lethal dose of radiation. In fact, it was later discovered, the donor cells replaced the host's ailing lymphoid tissue thereby protecting the immunologically paralysed animal against overwhelming infection. It was found, further, that once this immunological factory had been accepted, the host was in a position to accept any number of grafts of any type of tissue from that specific donor. Similar results were obtained when rat hemopoietic tissue was injected into the irradiated mouse, resulting, in effect, in the production of successful heterotransplantation. However, though this state of affairs may at first seem to be a happy marriage of two populations of antigenetically different cells, the situation, in reality, is not rosy. While the host complacently tolerates the hemopoietic transplant, it is the latter that throws a wet blanket upon the merry symbiosis. It appears that the immunologically competent cells of the donor rebel against the tissues of the host, which proves to be a short-sighted procedure, since the host often goes on to die carrying with it the rebellious transplant.

B. AGAMMAGLOBULINEMIA.

A discussion of agammaglobulinemia, here, is only relevant in that it is one of the conditions

which sometimes allows the non-specific implantation of homografts. The agammaglobulinemic patient has received considerable attention in recent years, though the amount of work done to-date does not allow the formulation of general principles. On the basis of etiology, the condition may be subdivided into at least three categories (6):

1. Congenital agammaglobulinemia.
2. Acquired agammaglobulinemia.
3. Transient agammaglobulinemia ("physiological" in the premature infant.)

It has now become apparent that congenital agammaglobulinemia is not synonymous with a simple lack or deficiency of the gamma globulin fraction of serum, but is a complex immunologically deficient entity where the abnormal gamma globulin level is but one of the manifestations. The condition is of interest here, because cases have been reported where successful skin homografts (and kidney grafts) have been achieved from a normal subject to an agammaglobulinemic patient. Before more was known about homograft reactions, it was tempting to assume that grafts were successful because the patient was unable to develop circulating antibodies. Now it is thought that the relationship between the gamma globulin deficiency and the failure to reject a homograft is a coincidental, rather than a causal one. This train of thought is supported by the fact that successful homograft acceptance has only been reported in patients with the congenital form of the disease. The scant evidence which could be derived from the post-mortems of six congenital agammaglobulinemic children who died of unrelated causes suggests that there is a general depletion of the whole lymphatic tissue population in this form of the disease and grossly lymph nodes could be detected in only a few patients, which might indicate that there is more wrong with the congenitally agammaglobulinemic patient than lack of circulating antibodies. Another piece of evidence suggesting that homograft acceptance is not causally related to gamma globulin deficiency is the report of Medawar (1955) who states that foetal sheep known to be agammaglobulinemic at birth are capable of fully rejecting homografts long before birth. Therefore, it may be concluded that gamma globulin deficiency, per se, is probably not responsible for the failure of homograft reaction.

Another puzzling situation brought to light by the study of the agammaglobulinemic patient is that some of those patients who accept homografts are yet able to display acquired cutaneous hypersensitivity of the delayed type (8). If this observation is confirmed by the study of more cases, it may eventually intimidate the pleasingly

unifying theory to the effect that the homograft reaction and delayed hypersensitivity are fundamentally related phenomena.

It was hoped at one time that because some agammaglobulinemic patients did not reject homografts, they might be induced to accept lymphoid tissue for a normal donor and thereby become re-equipped with a functioning, borrowed immunological apparatus. That this might be a possible cure for the condition was suggested by animal experiments since, as was previously mentioned, mice withstand potentially lethal doses of radiation (which renders them immunologically paralysed) provided they are subsequently re-equipped with homologous marrow. So far, there is one report of a congenitally agammaglobulinemic patient who has been equipped with lymph nodes from a normal person, but the clinical improvement, if any, was questionable (7). Recent experiments with mice (1) demonstrating that homologous lymphoid tissue transplants could react against the host, sometimes even causing its death, makes this line of approach somewhat less promising.*

4. SPECIFIC MEANS OF WEAKENING THE HOMOGRAFT REACTION.

A. ACQUIRED TOLERANCE

(i) *Introduction:*

Though, possibly not in the best of scientific tradition, it might be interesting to begin discussion of acquired tolerance with a few words of teleological speculation. Why is an animal so stubbornly intent in avoiding tissue implants of his brethren? Surely, in the normal course of events an opportunity for a homograft response never arises and, if it does, it is only during fetal life through placental transfer (and this is very rare, if at all existent) at which time there is not the trace of rebellion noted. Further, it is unlikely that this competent immunological defense, had arisen as a result of Nature's foresight to thwart man's meddlesome interference. Most weekend teleologists postulate that the homograft response is but a fortuitous extension of a mechanism primarily designed against bacterial (or viral or protozoal) infection. But, then, it is not even known whether bacterial hypersensitivity is desirable to the animal since the side-effects of this mechanism can be more damaging than

the infection itself in the non-hypersensitive animal.* It may be argued that if the homograft response were studied before hypersensitivity, one would be inclined to say that hypersensitivity was but a 'fortuitous extension' of the homograft response.

A new explanation for the existence of the homograft response has been offered. It has to do with the universal requirement of the multicellular organism to preserve the uniformity of its cells, and to prevent mutant cells from flourishing and colonizing the organism. This is a postulation to the effect that the multicellular organism against neoplasia. Some support for this line of theorizing is the apparent tendency of certain individuals to develop multiple malignancies — which might reflect upon a general inability to deal with neoplasia. As a support to this observation is the recent demonstration that cancer-bearing patients do not react as vigorously against other patients' malignant cell transplants as do normal individuals (16). Dr. Lewis Thomas, from whose discussion most of the above was apologetically lifted, has yet another interesting idea concerned with the possible teleology of the homograft response. This postulates an immunological rejection of the placenta as the determinant of the time of parturition, (the placenta being in effect a fetal homotransplant in the mother). (see "Clinical Application".)

Having suggested some reasons for the existence of the homograft response one is in a better position to approach an outstanding method of experimentally abolishing this mechanism. Certain relatively inefficient, non-specific methods have already been discussed. However, a far more fascinating approach, which abolishes the homograft response specifically with respect to a certain donor, is that of acquired tolerance.

It has been known for about fifty years that dizygotic cattle twins, who were able to accept each other's homografts, were almost invariably nurtured by a synchorial placenta which permitted admixture of the twins' blood. This state of naturally occurring tolerance was known to Burnet and Fenner who formulated the "self-marker" theory, postulating that organisms in the process of development must "learn" to recognize their own tissues and that this process of learning occurs in a certain span of time and is not a spontaneous, inherent state of affairs. Thus, it follows, if antigens were introduced into the young animal, during its immunologically for-

* The possibility presents itself of preventing a graft vs. host reaction by previously rendering the donor's cells tolerant to the prospective host's tissue. The possibility of inducing tolerance in the newborn human infant with the prospect of making him a future donor to an agammaglobulinemic patient might be a promising approach, though it is probable that years of animal experimentation and elucidation of the phenomenon of tolerance would be required before this approach could be put to the test.

* Bacterial hypersensitivity refers to 'delayed' (tuberculin) type of hypersensitivity. No one would argue against the protective value of the 'immediate' type of anti-bacterial immunity mediated by circulating antibodies.

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mative years, they might be expected to become accepted as "self"-antigens.

(ii) *Induction of Tolerance:*

From the study of a number of animal species, it may be concluded that the developing animal goes through three immunological stages. For our purposes, these may be termed the adaptive phase, the neutral period and the mature phase.

a) Adaptive Phase

It should be mentioned at the outset that immunological development is not necessarily correlated with the time of birth. Tolerance may be induced only during the adaptive phase, which, however, may terminate before birth as in the sheep or cattle, or some weeks after birth as in the rat. Also, termination of the adaptive phase seems to vary with the type of antigen used in the induction of tolerance. Indications are, that the more distant the phylogenetic relationship between antigen and host tissue, the sooner the adaptive period terminates with respect to that antigen.

Theoretically, there is no "early limit" to the induction of tolerance, and such a limit is only set by technical considerations and the act of interfering with normal embryonic development. However, a very definite time limit exists as to how late the antigen is introduced. This is determined partly by the species, by the relationship of antigen to the host tissue and partly by individual difference.

b) Neutral Period

If antigen is introduced into the animal after the termination of the adaptive period, tolerance is no longer induced, but if the material is injected before a certain critical period, immunity is not induced either. That is, such an animal, when subsequently challenged with the graft of the donor to whose cells it had been exposed before, will react with the characteristic primary response. This neutral period, then, is an immunological no-man's land characterised by the development of neither tolerance nor immunity.

c) Mature Phase

Once the neutral period is over, injection of the donor cells produces a state of immunity, as in the adult animal. That is, subsequent transplants elicit the accelerated type of response characteristic of second-set grafts. This is the type of response that persists from the termination of the neutral period to the animal's dying day.

(iii) *Mechanism of Acquired Tolerance.*

While in the above discussion the word "antigen" has been thrown about rather loosely, it should be understood that most of the work in this line was done using living cells. Thus, it is not known (1956) whether introduction of non-living cell preparations injected in the animal's adaptive period would be capable of producing tolerance to subsequent living grafts from that donor. On the contrary, experience to date seems to indicate that success of tolerance induction depends on the viability and structural integrity of cells used in the initial exposure. In fact, from data available it could well be that the injected cells remain viable and proliferate in the host actually taking over the immunological responsibilities of the host. This could easily occur since, at that stage of its immunological development, the host would be incapable of defending itself against these cells.* One fact that may, or may not, be relevant, is the recent demonstration of "runt disease". This is an experimental condition which occurs when a homograft is implanted into a newborn animal (in the "adaptive phase"). It is thought that the immunologically competent cells in the graft proliferate in the defenseless animal, replace its lymphoid tissue and proceed to destroy the host by way of a parasitic graft against host reaction. Whether an analogous situation would occur in all cases of attempted induction of tolerance is a question that has not been settled.

Whether the cells used for tolerance induction actually re-populate the host's lymphoid tissue or act by way of some yet unknown mechanism, it is relatively safe to say that there occurs a cellular transformation resulting in the blockage or deviation of the normal immunity production pathway with respect to the specific antigen. Also, since tolerance is long lasting, it follows that the transformation is inheritable (from cell to cell) and transferred to the entire immunologically active cell population, because, if this were not the case, any remaining immunologically potent cells would be available to destroy the graft. Alternatively, it might be questioned that the interference in the production of the response might not be due to a peripheral type of interaction. One might also postulate that possibly

* If this were the case then it would probably be futile to attempt production of anti-cancer antibodies through inoculating malignant cells into an animal previously rendered tolerant to the donor's normal tissues, since such an experimental set-up would merely provide a new medium for the patient's usual immunological expression, which is thought according to this theory, to be defective in the first place. On the other hand, the possibility exists that this new medium might enable the donor's lymphoid cells to achieve a normal immunological response, particularly if the malignant cell in the patient's body exercised a malevolent effect on them.

through the induction of tolerance there develops a line of cells which prevent the execution of the homograft reaction by preventing the immune cells from acting on the graft. That this is not the case has been proven by Billingham and others, employing a series of ingenious experiments based on the rules of experimental transplantation. However, to avoid complications, Billingham's experiments will not be dealt with here, but the essence of a similar experiment is as follows. If a mouse tolerant to donor A is injected with lymphoid tissue from a normal, unrelated mouse, it is seen to regain its capacity to respond against a graft from donor A. Of course, it must be remembered that the lymphoid cells from the unrelated donor will excite a homograft response in the host against themselves, therefore, the rejection of graft A is not complete, ceasing as soon as the injected lymphoid cells have been

clearly demonstrates that if immunologically potent cells are present, they can act, thus showing that the interference of homograft response in the tolerant animal is not due to peripheral interaction. A state of borrowed immunity in the tolerant animal is termed "adoptive immunity" and has proven to be a valuable experimental tool.

(iv) *Special Types of Acquired Tolerance.*

a) Maternally induced tolerance.

Since tolerance can be conferred by injection into the fetus of very small quantities of cells, it is not unreasonable to expect that a few maternal cells would occasionally slip into the fetal circulation. Since guinea pigs have a comparatively prolonged period of gestation (providing a greater opportunity for passage of maternal cells), maternal homografts have been studied statistically in this animal. Two, of the fifty animals studied, displayed tolerance to maternal grafts. Although this is somewhat inconclusive, it does suggest that the incidence of placental slip-up is not great.

b) Tolerance to Malignant Cells,

Experiments indicate that tolerance of malignant cells can be successfully accomplished. It has also been shown that animals tolerant to the tumour cells could be made to accept normal homografts as well, indicating that the normal tissue did not possess an antigenicity over and above that of malignant cells. However, this does not prove that the reverse could not be the case.

c) Tolerance to Heterologous Antigens,

Acquired tolerance to heterologous tissue is only partially successful. Prolongations of graft survival have been achieved but not permanent "takes". Even heterologous malignancies of the

greatest *elan vital* could be grown only after serial passage through embryos and the brain tissue of very young mice. After this, however, the malignancy seemed to have lost most of its antigenicity and could be grown in normal mice eventually causing their death (13). Though this might, at first, appear to have teleological repercussions — namely, that the tumour became less antigenic in order to survive in antagonistic hosts — an alternative explanation has been proposed. It may be that during the reproduction of tumour cells in an antagonistic medium, those mutant cells that had lesser antigenicity would be favored in their multiplication at the expense of the less fortunate, producing, in effect, a type of Darwinian selection in miniature.

Studies of tolerance have been extended to other types of antigen. Thus various degrees of tolerance of a bacterial organism Rous sarcoma virus and even of a protozoa antigen were produced. While, to date, it has been impossible to produce complete tolerance to living heterologous cells, it has been shown in rabbits that a state of complete tolerance can be induced toward non-cellular heterologous protein.

B. IMMUNOLOGICAL PARALYSIS.

There are certain other means of specifically weakening the immunological response to an antigen, but it is not yet known whether these have any relationship to the phenomenon of acquired tolerance.

It was shown in 1949 that, whereas small immunizing doses of pneumococcal polysaccharide serve to protect an adult mouse against subsequent injection of potentially lethal doses of living pneumococci, a large dose of the polysaccharide would enable otherwise sub-lethal doses of the living bacteria to exercise a lethal effect. That is, while a small immunizing dose will increase the defensive capacity of the host, a large dose will decrease it. This latter action has been termed immunological paralysis and it resembles acquired tolerance in that it is long lasting and specific. However, it is now felt that the term "immunological paralysis" is a misnomer and that the effect is not caused by a specific depression of the central response but rather is dependent upon a peripheral interference with the execution of the response. There are indications that the effect is dependent upon the level of polysaccharide antigen remaining in the animal at the time of exposure to the live organism. Thus, it may be postulated that the polysaccharide antigen competes with the live organism for the available immunological response of the host.

C. INHIBITION OF DRUG ALLERGY.

It was discovered that attempts at dermal sensitization in the guinea pig are sometimes foiled by previous feeding of the same antigen. This is true only for certain allergens, such as picryl chloride, which are known to produce a delayed type of cutaneous response. It was noted that this inhibition was long-lasting, specific and that it could be abolished by transferring peritoneal exudate cells from a sensitized guinea pig which had not been previously fed the chemical. This indicates that the inhibition is not of a peripheral type because the borrowed immune cells are seen to perform effectively. It is therefore likely that the mechanism of inhibition of drug allergy is a truly central inhibition analogous to acquired tolerance but differing in at least one important aspect — that the latter can be induced only in the immunologically immature animal. Also since the allergy inhibited is of the delayed type, its similarity to the phenomenon of tolerance is a further indication of the suspect fundamental

D. PHENOMENON OF ENHANCEMENT.

There remains to be discussed one more interesting experimental discovery which fits into this classification of specific abolition of immunological responses. This concerns the phenomenon of enhancement, discovered in 1948, (3) when it was found that homograft tumours could be made to grow provided the host had been pre-treated by the injection of killed tumour tissue. studied using skin homografts instead of tumour tissue when it was seen that pre-treatment of the host with lyophilised tissue produced the somewhat less dramatic effect of merely prolonging the expected graft survival. Possibly, the initial work with tumour tissue was more promising because such tissue is known to have a greater vitality and is occasionally able to override the immunological defenses of the host.

The immunological depression was found to last about seven weeks in mice and the latest date of tissue-homogenate administration for a successful take was one day after implantation of the graft. The effect was found to be passively transferable by means of serum from the "enhanced" mouse (or even rabbit to a mouse) and the activity of the serum was seen to reside in the gamma globulin fraction. This phenomenon suggests the apparent paradox that circulating antibodies far from curtailing homograft acceptance seem to facilitate it. On the face of it, this has a marked similarity to immunological paralysis discussed above, where a large dose of pneumococcal polysaccharide enhanced subsequent invasion by the living cocci. A further

similarity is that, if live cells are used for pre-treatment, enhancement does not occur, just as when living pneumococci are used, immunological paralysis (apart from toxic effects) does not occur. Whether the similarity is real or apparent remains, at the moment, a prerogative of the educated guesser.

One explanation for the phenomenon of enhancement, stripped of adornments, states somewhat as follows. It may be postulated that the killed tissue homogenate competitively stalls the immunological defenses of the host by sacrificing itself, thereby sparing the living graft cells from the trauma of being engulfed by the host's immune mechanism.

5. CLINICAL APPLICATION. (4)

The ominous singular used in this heading suggests the relative sparsity of the presently available clinical addenda to the above experimental discussion. It is interesting that while most of the work has been done with the prospect in mind of eventually overcoming the homograft reaction, the first promising opening should come from actual utilization of the homograft reaction. The work presented in the following lines is the case report of a single case of choriocarcinoma which was apparently cured purely by a special application of the homograft reaction. This work was done by Dr. B. Cinader at the Princess Margaret Hospital, and his reasoning went somewhat as follows.

Choriocarcinoma cells arise from the fertilized egg and they are, therefore, not strictly autologous, deriving half their genetic complement from the male. Therefore, assuming that the male genetic portion of the tumour contributes to its immunological expression and also that the tumour tissue could be affected by antibody produced against normal tissue, the question arises whether an attack against the malignancy could be induced by reinforcing the patient's immunological defenses by providing antibodies against male tissue.

Assuming that these conditions are favourable, one is faced with the choice of actively immunizing the patient with male cells or alternatively using an experimental animal for the production of the antibodies and transferring to the patient a passive immunity. In 1958, circulating leucocytes of the husband were used to produce active immunity in the patient by subcutaneous injection, but the results were inconclusive because all the other available forms of treatment were administered simultaneously (5). Cinader decided to use both forms of attack, active and passive immunity, employing multiple routes of exposure for the induction of the active immunity, and at the same time withdrawing all other forms

of treatment once the immunological approach was begun.

For the passive immunization, he used the husband's sperm cells, since repeated supplies could easily be obtained and it has been shown that the sperm cell can induce tolerance in animals which is effective with respect to the donor's other tissues as well (9), indicating that the sperm cell was not deficient in any significant transplantation antigens. He immunized a number of rabbits repeatedly and for long periods in order to build up as high a titre of antibodies as possible.

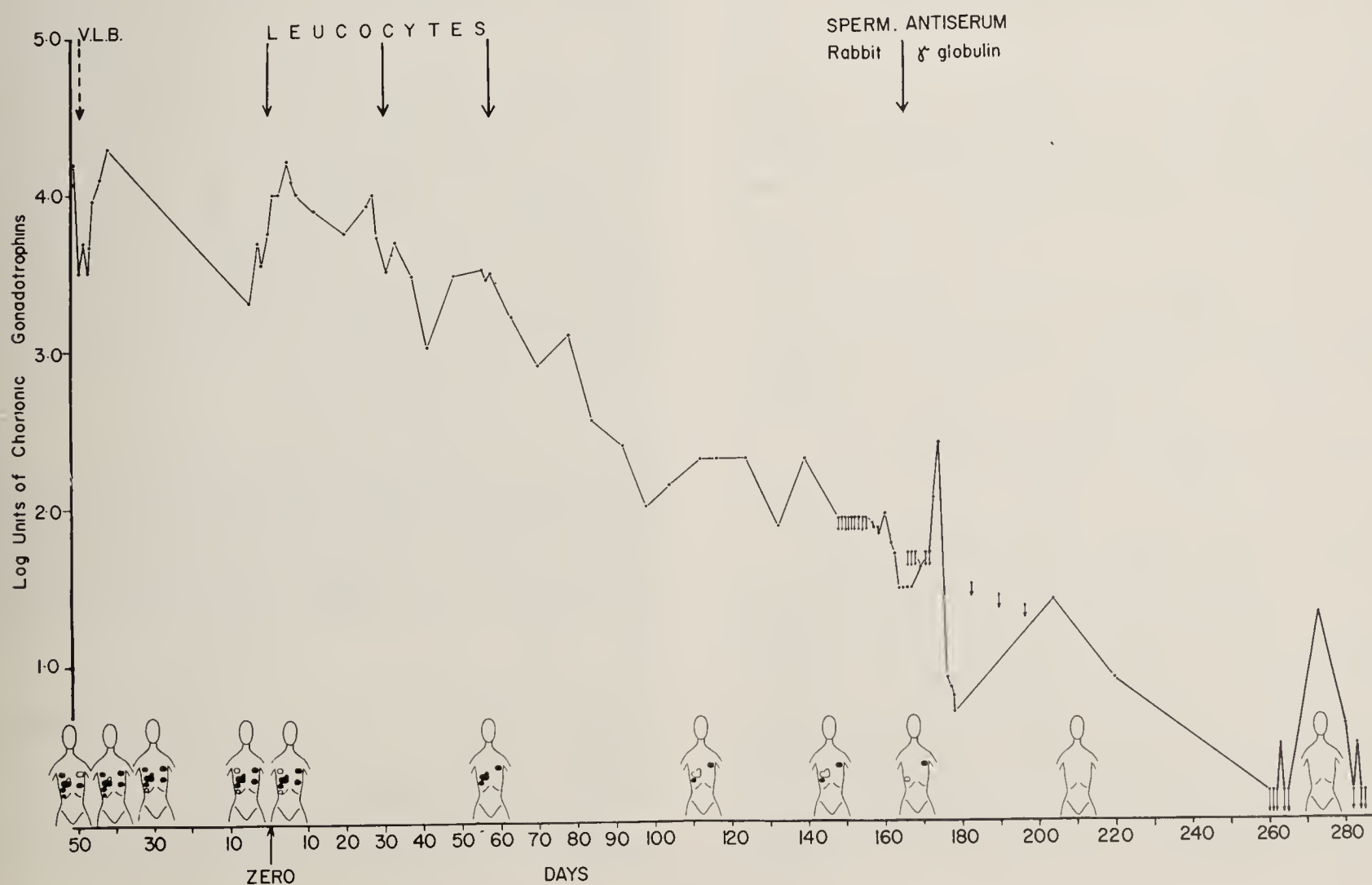
The patient prior to being exposed to this treatment had already had a hysterectomy and was being treated with V.L.B. (Vincalukoblastine sulphate, and antimetabolic agent), in spite of which, the condition progressed and lung metastases were demonstrable on X-ray. Dr. Cinader reasoned that the patient should first be treated with active immunization with husband's leucocytes while the passive antibody titre could be sufficiently increased in the rabbit to allow effective passive immunity to deal the final blow. He expected that positive proof of the anti-sperm antibodies' efficacy would be the observation of a temporary rise in chorionic gonadotrophin output soon after inoculation of the rabbit-manufactured antibody, signifying that cells containing this hormone were being effectively disintegrated. That this expectation was fully realised can be seen by studying the illustration.

Three doses of leucocyte concentrates were administered, subcutaneously and intravenously, following which the patient's CGT declined steadily and progressively. After about five months, when the rabbit antibody titre was at a peak, the gamma globulin fraction was isolated from the rabbit serum and exposed to normal human tissue in general. The purified anti-tumour gamma globulin preparation was then injected into the patient following which there was an immediate, sharp rise in the urinary CGT and the output then fell sharply. During treatment, X-ray evidence of lung metastasis disappeared completely and the CGT output dropped to normal levels. Whether the treatment was permanently successful is, as yet, too early to determine.

In order not to be carried along too far in one's enthusiasm, it should be realised that choriocarcinoma in the female* is a very special type of malignancy, on the following counts:

1. Following hysterectomy, patients with evident metastases sometimes improve, though to what extent and for how long, is not definitely known.
2. There is a general impression that choriocarcinoma is amenable to chemotherapy, and that about one in four patients improve permanently.

* Male choriocarcinoma is an autologous tumour.



TISSUE TRANSPLANTATION AND THE HOMOGRAFT REACTION

3. A variety of chemotherapeutic agents is effective.

4. The question of spontaneous remissions has been repeatedly raised, but there is a grave doubt whether a truly authenticated case has ever occurred.

These questions may be partially answered by the postulation that choriocarcinoma is a tumour growing in a highly antagonistic host, and that its antigenic peculiarity exposes it to a full blast of the host's immunological defense. That this defense is insufficient to defeat the invader could be credited to this tumour's extraordinary vigour. However, it may be further postulated, if chemotherapy, irradiation and hysterectomy or any other treatment is brought to the aid of the host, it is conceivable that the joint effort could suffice to overcome the tumour.

Then, one might ask, how can a normal pregnancy occur? Why isn't the normal fetal tissue rejected as it grows into the uterine wall? There is no answer to this question, but it might be reasonable to suppose that there is some protecting mechanism preventing the fetal antigens from arousing the host which is, however, broken down by the malignant neoplasm. If this were true, then the interesting suggestion might crop up, that the husband's leucocytes might be used to produce immunity in the faithful wife against normal fetal tissue, thereby serving as a means of birth control. As a corollary, it might be advisable to avoid fresh blood transfusions from husband to wife in the fertile age group.

SUMMARY

The purpose of this article reviewing tissue transplantation was to acquaint the medical student with a few aspects of a topic which promises to be an extremely important one in the not too distant future, and, to which the student has not been exposed in the course of his education. Because the field is in a state of rapid flux, it has been possible to present only a few simple generalizations. It was impossible to enter into some of the more detailed experimental subtleties, any one of which might from one day to the next become a major avenue of approach.

The fundamental aspects of the homograft reaction have been dealt with in some detail. It was shown that the antigenic individuality of tissues was governed by histocompatibility genes whose relationship to red blood cell groups, though real, was more of theoretical than practical interest. Certain physiological conditions in animals where homografts could be accepted were mentioned. The histological picture of graft rejection was reviewed drawing attention to the marked difference between first and second contacts of grafts with the host. The homograft

reaction was seen to be specific for the antigenic make-up of the individual in a species but did not differentiate between the types of tissue of the individual. A possible exception to this might be malignant tissue which may possess an additional antigenic component though it has been shown that the reverse does not hold unless the malignant cells are allowed to become altered (as has been reported occurring through repeated passage in weakly reactive hosts). The humoral and cellular mechanisms were discussed with the conclusion that cells were probably not essential for heterograft destruction but that they did exercise at least some effect in homograft rejection. Of methods used to allay the homograft response, some were seen to be non-specific in action, and, of these, only total body irradiation and possibly the naturally occurring human congenital agammaglobulinemia permitted total acceptance of homografts, while adrenal steroids were relatively inefficient, especially in man. Acquired tolerance was the most constantly reproducible method of specifically allaying the homograft response and because of its potential clinical promise, it has been discussed in some detail. The experimental animal in the course of its immunological maturation was seen, at a certain stage, to be educable with respect to subsequently accepting homografts from a specific donor, however, with the potential danger of graft versus host reaction. Other phenomena whereby specific acceptance of certain antigens could be induced, were briefly presented. Some very recent advances in the treatment of choriocarcinoma by means of induction of active and passive immunity in the patient were described, though based on the somewhat flimsy substantiation of a single case report.

In closing, it is important to emphasize that conclusions drawn from animal experiments and applied to man are held in low esteem. Therefore, every animal species must be regarded as a three-eyed toad before inferences are made crossing the species barrier.

ACKNOWLEDGMENT

I wish to thank Dr. J.L. Fitzgerald and Dr. B. Cinader for their academic assistance in the preparation of this paper; Mrs. H. Crowley for turning the Princess Margaret Hospital library upside down, Mrs. N.L. Blanchet for her syntactical aid and the staff of the science section of the University of Toronto Library who obligingly turned the other cheek when volumes were overdue (I hope).

BIBLIOGRAPHY

1. Billingham, R.E.; *Ann. New York Acad. Sci.*, 73, 3:782, 1958.
2. Brent, L.; *Progr. Allergy* vol. 5, pp. 271-348 (S. Karger, Basel/New York 1958).
3. Casey, A.E. *et al*; *Proc. Soc. Exp. Biol.* 69, 579, 1948.
4. Cinader, B., *et al*; *Canad. M. A. J.*; to be published.

5. Doniach, I., J. H. Crookston, and T.I. Cope; *J. Obs. and Gynec. Brit. Emp.*, 65, 533, 1958.
6. Gitlin, D., *et al*, Symposium #9, New York Acad. Med., Cellular and Humoral aspects of the Hypersensitive States, H.S. Lawrence, Editor, p. 375.
7. *Ibid.* — p.420.
8. Good, R.A., J.B. Aust, and S.J. Zak, *Ann. New York Acad. Sci.*, 64, 882, 1957.
9. Hasek, M.: *Biologie des Homogreffes; Colloq. Internat. Centre Nat. Recherche Sci. Paris. Vol. 78, p. 215, 1959.*
10. Harris, M., and Eakin, R.M.; *J. Exp. Zool.*, 112, 131, 1949.
11. Heslop, R.W., P.L. Krohn, and E.H. Sparrow; *J. Endocrinol.*, 10. 325. 1954.
12. Jones, P.F.; In "Preservation and Transplantation of Normal Tissues", (Ciba Foundation Symposium), London, p.196, 1954.
13. Koprowski, H.; *Nature, Lon.* 175, 1087, 1955; *Proc. Amer. Assoc. Cancer Res.* 2, 251, 1957.
14. Krohn, P.L.; *Ann. New York Acad. Sci.*, 59, 443, 1955.
15. Lorenz, E., *et al*; *J. Nat. Cancer Inst.*, 15, 1023, 1955.
16. Southam, C.M., A.E. Moore, and C.P. Rhoads; *Proc. Amer. Assoc. Cancer Res.*, 2, 251, 1957.
17. Woodruff, F.A. and H.G. Woodruff; *Phil. Trans. B.* 234, 559, 1950.
18. Corer, P.A.; *J. Path. Bact.*, 54, 51, 1942.
19. Hericourt, J. and Richet, C.: *De la Serothérapie dans le Traitement du Cancer; Compt. & End. Acad. Sci.*; 121, 567, 1895.

RECOGNITION AND TREATMENT OF OESOPHAGEAL PERFORATIONS

D.L. Paulson, R.R. Shaw and J.L. Kee: *Annals of Surgery*, July 1960, vol. 152, pp. 13-21.

Perforations of the oesophagus may be due to trauma (either direct or indirect), inflammatory and neoplastic lesions. However, perforation is more frequently due to trauma than intrinsic disease largely because of the increasing use of endoscopic procedures for diagnosis and treatment of oesophageal conditions. The procedures seemingly most hazardous are those for removal of foreign bodies and dilatation of strictures. Indirect trauma of the type associated with sudden high intra-oesophageal pressure transmitted from a full stomach in the act of vomiting is becoming recognized also.

The diagnosis is relatively easy if one is alert to the possibility of its occurrence. The main symptoms are severe pain, dysphagia, fever, and elevated pulse rate together with X-ray evidence of air or fluid in the neck, mediastinum, or pleural space following a history of foreign body ingestion, instrumentation, vigorous vomiting, trauma to the neck and chest or the presence of intrinsic disease in the oesophagus. The voice is often noted to have a peculiar nasal twang due to emphysema, and movements involving the spine are often painful. The differential diagnosis may be confusing if the perforation occurs in the thoracic portion and one must rule out perforated peptic ulcer, coronary occlusion, and dissecting aneurysm. Perforations due to missiles, stab wounds and surgical injuries frequently go unrecognized until signs of infection of the surrounding tissues supervene.

Recent experience shows that prompt surgical closure with drainage of the peri-oesophageal space, plus liberal use of antibacterial agents and general supportive therapy markedly reduces this to 20%. Instituting treatment even and general supportive therapy markedly reduces morbidity and mortality. It is felt that

this combined treatment is much superior to the more conservative drainage or antibacterial therapy alone. The mortality without treatment is 70% or more, while the recommended therapy reduces this to 20%. Instituting treatment even late after infection of the surrounding tissues has occurred, results in good healing and low morbidity. Primary thoracotomy, oesophagotomy and removal of a foreign body lodged in the thoracic segment before perforation occurs, is preferable to the more traumatic and dangerous endoscopic removal in an edematous and inflamed oesophagus.

NEONATAL T WAVE PATTERNS

L. Stern and J. Lind: *Acta Paediatrica*, July 1960, vol. 49, pp. 329-337.

While the T waves in the ECG taken within the first minute of life show good amplitude in all standard leads and V1, there is a definite tendency towards decreasing amplitude and flattening as early as 4 minutes of life. This change occurs in all infants regardless of clinical state and must be considered as normal. Factors implicated may be closure of the ductus arteriosus, rapid fall in pulmonary arterial pressure, or decrease in adrenaline output shortly after birth.

A PLETHYSMOGRAPHIC METHOD FOR MEASURING THE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN NEWBORN INFANTS

O. Celander and G. Thunell: *Acta Paediatrica*, July 1960, vol. 49, pp. 497-502.

To date, methods of blood pressure measurement in the newborn have been inaccurate and diastolic readings virtually impossible. The authors use a simple plethysmograph over the foot and calf to measure rate of arterial inflow while a sphygmomanometer occludes venous return proximal to the apparatus. The highest cuff pressure at which minimal arterial inflow is recorded must be the systolic pressure; the highest cuff pressure at which maximal arterial inflow is recorded must be the diastolic pressure.

SOME PRINCIPLES OF OFFICE PSYCHOTHERAPY

This article is based on a series of three lectures given for the first time this year to the graduating class by Dr. Mitchell.

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In this paper there is no intention to represent any particular school of psychotherapy or body of psychodynamic theory. Rather, I wish to express, in broad terms, the way that the average psychiatrist might look at psychotherapy when the body of theory subtending this sort of action, or possibly elaborating it, is reduced to a minimum. The issues dealt with do not cover the area fully but are, by and large, common problems.

A parsimonious *definition* of psychotherapy would be a "purposeful psychological interchange between the therapist (this may not be a doctor) and a patient with the specific goal of modifying some part of the patient's dilemma by this interchange".

Aside from the extreme physical aspects of medical practice such as surgery, the practitioners of medicine (those in internal medicine, general practice and pediatrics) have a large number of neurotic patients coming to them which they treat as best they can psychotherapeutically in order to do a thorough job helping a broad spectrum of the sick population.

The *demand* for psychotherapy is, and always has been, enormous. Unquestionably, this demand will grow as minor nervous illnesses are no longer seen as signs of weakness. Society's response, as it determines medical attitudes, has been more or less to neglect this aspect of mental care except for the privileged, usually the top 10% of our social class structure. It will be clear that doctors, in fulfilling such a small part of the demand situation, are outnumbered by clergymen, chiropractors, mothers-in-law, sisters, friends and neighbours. Ironically, the physician is the ideal therapist insofar as he does not have a personal relationship with the patient nor need he indoctrinate him with either his values or belief system. This preferred position is threatened by our neglect of the majority — need which will be met by other disciplines should we continue to ignore it. There are some people that say these other groups should, in fact, take over the major portion of the psychotherapeutic task and the tendency for this to be done is increasing.

The fact that psychotherapy is so widespread and in such great demand in no way affects its efficacy. Generally, it can be said that when psychotherapy is subjected to statistical approaches with both control and experimental groups, it has been found of questionable use to patients.

Statistically, this is tenable despite the belief physician and patient might share that improvement has occurred. However, it can be illustrated in numerous ways that such studies as those carried out to date are fallacious. Close examination of both subjective and statistical measures and their shortcomings make it quite clear that one human can influence another for the better. The technical aspect of this influence is yet unsolved for it would seem that most of the popular psychotherapeutic approaches produce only marginal benefits. Pragmatically, it must be remembered that psychiatrists and all other physicians are at the head of the list of people to whom psychotherapeutic demands are made and it is therefore incumbent upon us to work towards the perfection of technique.

Does psychotherapy take a lot of time? To the degree that clinics or doctors draw incorrectly from the population and produce sampling errors, one could assume, from the literature, that psychotherapy is an extraordinarily time-consuming procedure. In broadening the sample by going to out-patient departments of general hospitals or into the office of the general practitioner, the picture changes considerably. When the patient is properly selected for psychotherapy it would seem that almost 90% of this broader sample require no more than four interviews and in fact take up very little of one's active time in practice. The remaining 10% are more or less the "perpetual patients" who present considerable difficulties and account for more of the clinic or physician's time than the previous 90%. As a conservative suggestion, it can be said that if the patient is not better after 4 — 10 interviews, the physician may either be wasting his time or the patient might benefit more from other sorts of treatment.

When it is more broadly defined, psychotherapy consumes more time than any other activity in the practice of general medicine. Nevertheless, surprisingly little instruction in it is given to undergraduate students and this for the very good reason that no single technique, or number of techniques, has been found to be generally acceptable or teachable. Therefore, psychotherapeutic behaviour is as variegated as are people's personalities. For this reason, it is difficult to suggest to you how your psychotherapy should be carried out but, if you continually examine your thinking and your behaviour in the light

of the need to help the patient, a good deal of elaborate intellectualizing can be dismissed. If at one time you have a clear notion of the dilemma the patient is facing you should search rigorously for contradicting as well as affirmatory evidence for your theory.

THE INITIAL INTERVIEW.

This is one of the most difficult occasions in psychotherapy. Considering that it represents a meeting of two people who have not known each other before and yet have to talk about important concerns for an hour or less, it is not surprising that this initial interview has received a good deal of attention without any consistency other than it would seem to be important to make the most of it. For instance, if a patient came to you having already gone through the sequence "there is something wrong with me, I am nervous, I am not ashamed of being nervous, I want to do something about it, I will do something about it, I am now in your office," etc., a good deal of the initial interview problems ordinarily encountered are already solved. Initial interviews, on the other hand, become very complex when the patient is convinced that he has a physical disability, is making some social use of his physical complaints, when his ability to communicate is seriously impaired, or if he views nervousness as a denigrating admission. None the less, a frequent occurrence is that the patient will come complaining of his physical disability and, after being allowed to talk spontaneously for ten minutes or so, he begins to tell of his personal problems in life and often seems to forget his physical complaints. Do not rely on this. The point where you decide that his physical complaints do not warrant physical investigation is a personal one and rather arbitrary, and it is doubtful if there is any agreement at all, nor should there be, on whether physical investigation is a *sine qua non* of a visit to a doctor.

The primary aims of the initial interview include the assessment of the patient and his complaints, a delineation of his motivation in coming to you and an estimation of the capacity of this person to respond to the limited one-to-one handling that is entailed in office psychotherapy.

Some of the *conduct* of the initial interview, as well as subsequent ones, is so obvious that it reaches general agreement. One should not see the patient with a waiting room full of other patients and the telephone at your side waiting for possible emergencies. Instead, the patient should be given an appointment for a time convenient to each of you, but without too great a delay, when you can attend to him, and to him

solely, for 45 to 60 minutes. It may happen that at the end of this initial interview the patient may just be beginning a fuller description of his life problems. This is not an indication for prolongation, but for the question, "Could we go on from there next time?" It has been found that if the patient says too much he feels too ashamed or foolish, subsequently to return. On the other hand, the interview should not be under 45 minutes for it often takes people that amount of time to build some confidence to describe or even mention a few important things and get used to talking to you in this way. Your essential purpose in all early interviews is to be a good listener, to find but seldom remark on inconsistencies, and to restore to the patient some feeling of self-esteem, the loss of which inevitably accompanies his presentation to you. The patient comes to you tense, hopeful, full of feelings of inferiority, and is ready and willing to make you a supreme authority and an ideal sort of "father". Whereas this puts you in a very advantageous position to help the patient, it does for the same reason increase the chances of making mistakes. Eventually, it is hoped, each of you will be able to relate equally and, to do this, it is important to let the patient tell his own story as much as possible so that you can respond to him appropriately. This recounting is most frequently within his ability as he, at least, has a very clear notion of what is bothering him most. Interrogations into his school and family history or into his sexual behaviour often seem, to him, to be out of place and, if your goal is psychotherapeutic, they usually are. Concomitantly, it is important not to indulge in "pat" interpretations or explanations or to give the patient any theoretical material which you may have assimilated. At the beginning, a few notes made as the patient talks upset very few but, if it does, one should cease immediately. It should be possible for a patient to be in a chair beside, but not too close to you, or in a chair across a desk from you; patients prefer differing "barriers" from the doctor. Also they may like to shift or you may wish subsequently to shift. Because psychotherapy very frequently takes place towards the end of a working day and the physician may feel sleepy, any tendency to yawn or to inattention because of fatigue should be made explicit immediately and another appointment made with the patient as soon as possible.

Never argue with a patient or try to impress him in any way. The temptation to use small lectures in living or on the autonomic nervous system or the use of any deliverances similar to these to communicate your understanding to the patient should be controlled and avoided; they are seldom of use. Because we have our own per-

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sonal standards, it is sometimes impossible not to be implicitly disapproving of patients but this diminishes in time and, in that interim, it is important never to be explicitly disapproving. When the patient is being critical of himself, do not give any evidence of your agreement with him, nor should you ever go to the opposite extreme and play the devil's advocate. In quite accepting tones, you can point out to the patient that such censure is a feeling that he has about himself and one that you do not share. It is important never to talk about yourself unless it will clearly make the patient feel that his life experiences are not unique. That is, you could admit that all children are "nuisances", his, yours and everyone else's, but detail serves no purpose and the communication of things more personal is essentially resented by the patient and is of no value. The reason for this is that neurotic disorders do increase egocentricity as does the psychotherapeutic situation itself and these together do not allow any sort of social exchange or comparison.

The *methods of facilitating the patient's unburdening* are many, and some are rather obvious. Certainly, both parties should be comfortably seated and glaring lights do not help the patient release what are, to him, embarrassing confessions. If he wishes to smoke, he should be able to. A nodding of the head, a look of concern, a movement of the hands or a shifting in the chair, or of the chair, are wordless ways for you to tell him to continue in the present vein. By the same token, immobility and an expressionless face with averted eyes will tend to shift him from clearly unimportant detail or anecdote. Verbally, his communication can be furthered by asking him to enlarge on his last statement, by picking up a key word and merely repeating it with a slightly questioning uprise of the voice, or by the various sounds with which we punctuate our friends' conversation when the topic is very interesting. If silence develops, it is essential to ask him if he has difficulty in talking and it is quite legitimate to spend many minutes on this disability which may be much more important than gathering data. Prolonged silences (over two minutes) reflect either bad technique or poor patient selection and indicate the need for a standard psychiatric history.

There are some important things which one must find in the initial interview and which are handy methods of *terminating the first hour* even if the patient is only beginning to communicate easily. Does this disability affect his work and to what extent has it placed him in jeopardy? Has his disability seriously interrupted his social or home life? Is he losing weight because of a

poor appetite, is he unable to sleep or is he taking sedatives because of insomnia? To what degree does he resolve his anxiety with alcohol? If the picture is in any way depressive, if there is considerable social isolation or if the intake of alcohol and drugs is a remarkable one, a suicide assessment must be made. If there are enormous difficulties in any of these areas, they cannot be dealt with easily in the initial interview but can be mentioned as a desirable topic for the next discussion, the timing of which can be made more proximate the greater the difficulty. Some gentle reassurance at the end of the first interview is certainly in order but a reassuring attitude will or will not have already been communicated by the general way you have handled the interview. *Make no promises* — "I'll tell you as soon as I know" — is a good response to a prognostic demand at any time since you will never know.

'TRANSFERENCE'
and 'COUNTERTRANSFERENCE'.

It has already been stated that the patient is tense and therefore may produce a muddled account of his problem. Questions such as, "What do you mean by that?", serve to clarify for you, and for him, his present dilemma. They also serve to improve his ability to communicate with you and, to the extent that both these happen and you are careful about his feelings of inferiority, a good positive relationship can be established in the first and second interview which will go a long way to alleviate his anxiety. As time goes on, what began as a simple relationship very frequently evolves into a much more complex and meaningful feeling for each other and this is where, used in their broadest meaning, the words transference and counter-transference have been used.

"Transference" itself has no agreed definition even among doctrinaire schools, but may be described as a feeling that the patient develops toward you which should ideally be determined by him and not by you and often represents neurotic and early relationships to authority. It is usually quite intense and this is not undesirable for it often seems related to the efficacy of treatment. The intensity poses problems when it colours all his communication; e.g., if he feels you are a punitive father he will continually scan your verbal and motor output for criticism where none was intended. This is why you may have to appear (and therefore feel) on his side without exactly joining him in arms for the beginning interviews.

"Transference" in the doctor or therapist is called "counter-transference" and is receiving more and more attention nowadays: it is a feeling

you develop toward the patient and has importance both negatively and positively. This, above all, has to be continuously checked in case it demonstrates itself in non-verbal ways or even indirect statements which are deleterious to the reason the patient is coming to you. Excessive fondness, excessive dislike and excessive boredom are probably the most common early counter-transference manifestations; their deeper meaning will be individual. This automatically raises the question whether all physicians are suited to psychotherapy. It is wholly unlikely that all of us are suited for any one thing that can be mentioned except possibly getting through medical school and it is presumptuous to assume that all doctors have to do psychotherapy. However, it is certain that most of us do do it in, at least, a limited way and that our profession and its choice more or less selects people who are potentially capable of it. If a doctor dislikes psychotherapy, it is well that he does not do it. *Better* he learn why he does not want to do it and whether he wishes to correct this bias.

A lot of damage can be done by becoming over-involved with the patient. Immediately the physician loses his minimal subjectivity, there is a question of who needs whom. If this over-involvement becomes excessive and is recognized by you, it will often be diminished by that very recognition; if not, then both you and the patient would benefit from transferring the patient to another physician or specialist. This sort of involvement tends to diminish with experience.

PROBLEMS.

Aside from the difficulties of transference and counter-transference, there are specific events which can occur in psychotherapy making the actual process less successful. There are those who routinely arrive 35 minutes late and some, arriving on time, refuse to talk until the last 5 minutes of the appointed time. Lists of self-adjudged important topics notated mentally or on paper may be presented, frustrating the therapist's better intentions for the interview. Similarly, the patient may demand instructions as to the nature and curative measures of his illness, exhausting the available time. Further, there is the individual who consistently arrives for interview on the crest of 4 or 5 drinks creating an obvious disadvantage.

Progress is hindered where the patient is excessively aggressive or where he makes you into a romantic, if not sexual, figure very early in the series. Also, there are some patients whose inability to communicate verbally is considerable even though they may do a lot of talking; for example, the insincerities of statement in the hy-

sterical personality. Here, it is necessary for the physician to be an almost equal participant in exchange with them but this cannot be direct — it has to be oblique and subtle. The only alternative to this is to keep utterly silent until the patient runs out of mileage. Obviously, all of these problems need separate consideration.

One of the thorniest problems in psychotherapy is the very ambivalent patient, the one who wants to come and yet behaves as though he does not. This is one of the major causes of failure in office psychotherapy and unless overcome within two months or so, this patient should probably be referred. There are also those patients whose benefits from being "sick" are much more pleasurable than the joy they have living a healthy life. The psychotherapeutic change needs the appropriate attitude: these people do not have it; generally, they should not be taken after the clarification of this tendency.

PHYSICAL CONTACT.

There are many theoretical ideas about the degree of physical contact one should have with a patient, including spatial relationships, most of which reflect more dogma than fact. There are a number of people that say you should not do psychotherapy on a person on whom you have done a physical examination yet this obviously has to be overlooked, and can be safely, when a physical examination is clearly indicated. Do you open the door for the patient? Do you stand up when he comes in? Do you shake hands at the beginning or the end of the interview? Do you help the ladies on with their coats? Do you offer them cigarets? Do you accept their cigarettes? Do you accept presents? A number of these may seem trivial to the physician but to the patient they are often-times loaded with meaning. Nevertheless, general rules should not be made because of the variation in patient needs. A close contact may be needed for one throughout, or for another a short time and a considerable distance always clearly indicated for a third patient. It is of greatest importance not to extend the do's and don'ts of psychotherapy into rituals which must be carried out at all cost. Your behaviour should be tailored to the individual and to your abilities to collaborate with him.

Because of the nature of their psychological disability as well as the general inefficiency of the patient, money and the discussion of payment to you will often be a problem for the patient. This is considerably compounded by a physician who has the same difficulty dealing with apparently "crude" considerations when delicate emotional problems are being discussed. Our present economic system makes such a dis-

tation of the transference, etc., have a certain fashion. All these events can occur without your behaving in any other way than has already been mentioned and they seem to be part and parcel of the dependency that the patient develops toward you while he resolves his problems. Once these are resolved he then moves to an independent position. There are some indications that the whole range of change, in emotions, feeling, thinking and relating which are evident during a course of psychotherapy, can be undergone by a patient quite spontaneously and outside the therapeutic situation as he recovers at the end of the natural course of his illness.

TERMINATION.

After the symptoms are resolved, it is difficult to ascertain an appropriate time and method of terminating psychotherapy. Generally, the sessions should be stopped slowly by spreading them out or by shortening them, or by both, and an occasional inquiry about the desirability of stopping them be made to the patient in such a way as not to indicate a rejection of him. In a thoroughly successful situation, the patient will spontaneously dismiss himself from further sessions, to which you should give agreement but add that you will be available if necessary. Where the patient has not improved or where his relationship to you has become as important as the symptoms were, there are two practical courses (though there are many ideal) to be pursued. Where there is no improvement a referral to a specialized group is probably called for unless you have a particular interest in long-term psychotherapy. Where the relationship becomes a very neurotic one, you can usually forcibly diminish the frequency of the interview, make them less lengthy and sometimes a planned cancellation or two will alter the relationship without recreating symptoms. With the latter course you risk having the patient become angry with you but this is usually only a temporary phenomenon; he or she will turn affection toward another person. In the end, they will still come to you with their sore ears, throats and coughs as well as further neurotic problems.

SUICIDE.

The assessment of suicide is essentially that of a social and sociological background with a symptomatic foreground. Study of these reveals the suicidal risk as a man of Protestant faith (that is, of a less cohesive society) who lives in a downtown area and has recently moved. He has very few people or institutions or values to which he feels attached and, if married, most often has no children but, when he does, has less than the

norm. Using drugs and/or alcohol to excess normally, he kills himself early in the morning under the influence of alcohol with barbiturate overdoses, razors or bullets. Like the man with duodenal ulcer, he chooses the Spring and Fall seasons for expression and similarly, in the majority of cases, he does not suffer from any distinct psychiatric disturbance. Of the 40 odd percent that do have psychiatric illness in its formal meaning, agitation, hypochondriasis, insomnia with great concern about it, self-blame and already-expressed notions, if not attempts, toward suicide are the most common of the depressive symptoms indicating suicidal potential. Also, it is quite possible for schizophrenics to suicide. Its probability increases per capita with every year of age and the successful one has a certain efficiency about it that the gestured seldom has. The suicide gesture is more characteristic of women and is currently seen, in the literature, as an attempt to bring about a radical alteration in a deteriorated inter-personal dilemma.

USE OF DRUGS.

Pharmacologic treatment running concurrently with psychotherapy definitely has a place in a number of cases but, despite this, there are cases who should not have any drugs just as there are cases who should be receiving drugs and no psychotherapy. The drugs most frequently used are sedatives, tranquilizers and energizers. The sedatives should be used sparingly and in minimal doses but a good night's sleep is crucial to a neurotic depressed patient and this must not be ignored because of doctrinaire belief. Tranquilizers are now becoming more subtle and no longer deaden the person to all stimuli which might make psychotherapy workable but rather enhance it and are frequently useful, but temporary, adjuncts to a psychotherapeutic program. By the time one reaches the stage of mobilizing the energizers, it can be questioned whether anything but supportive psychotherapy is to be commended, for, if they work, they alter life's scenery as much as a blazing sun does after a short shower. There are people whose brittle sense of integrity does not allow them to happily submit to medication and one can go along with this unless it is clearly unsound, at which time you should use your authority to persuade them to take a chemical for a short period of time.

Over-dependence on drugs can be easily gauged if you have the confidence of the patient, if you are his sole supplier and if you do not become moralistic about the intake. Once again, the recommendation is for flexibility as the individual occasion demands and your attitude to

SOME PRINCIPLES OF OFFICE PSYCHOTHERAPY

cussion mandatory and it should be carried out as soon as possible so that their financial obligation to you and your psychotherapeutic obligation to them becomes clarified. Thereby, indebtedness need not interfere with the relationship. If the psychotherapy is prolonged, it can be a very expensive procedure and it demands a sliding scale according to the income of the patient and the demands on it.

RELATIVES.

Frequently, one of the most difficult problems in psychotherapy is the management of relatives, and this is best seen in problem marriages, teenage emancipations and in the disturbed child. A large variety of action is open to you in dealing with relatives but these should be determined by the need of the patient and his social *milieu* and not by your doctrine. Within this, relatives can easily be managed and the problem raised by marriage difficulties and by the secret call from the secret relative will be dealt with, as well as the situation when it is evident that it is not the patient but his relative that you should be seeing. There are other situations where the patient sees you as a confessor and can use you only to the degree that you do not communicate to anyone that you are, and deny any knowledge of, treating him. For the average patient, necessary communication with relatives through your instigation should be cleared by him before you proceed. When information flows spontaneously from relatives to you, the handling of such communication is very individual. Never make an interview with a relative without the explicit consent of your patient. Eventually, when the patient feels that you are distinctly on his side and not critical, that is, he feels accepted and trusts you, it will make little difference to him whom you see about him providing professional confidence is kept to the degree that the patient would wish. All this reasoning breaks down quite quickly in the psychotic patient and in a number of drug addicts, alcoholics and some criminals, but it might be noticed that office psychotherapy is least effective on these people in any case, though it is sometimes impossible to avoid.

COMMUNICATION FACTORS.

It is unfortunate that when a person comes to listen to another talking about his problems, he comes with notions about what is important in life and what is not. One physician may think that sexual problems are the only relevant ones, another may feel that it is a breakdown in a social pattern which is crucial in the formation of an illness and another may place greatest emphasis on dependency and hostility. This frequently leads the physician into a position where

he ignores those areas that are important to the patient but not important to the physician, and an impasse becomes inevitable. What is most important is that you have enough knowledge of the cultural background of the patient to know what the probable values and behaviour are for his group and to be able to judge to what degree these values or behavioural patterns are exaggerated in your patient. In a way, the physician can do this more easily if he comes from a different social background but this increases the possibility of his being unaware of the poignant suffering that an unshared attitude produces in a patient. Sympathy to the various classes within our culture is gained, of course, from experience and, to a degree, from reading. The doctor may lack knowledge of the patient's cultural background but the importance of what he says may be shown by his movements, his facial expressions, his verbal repetitions. A relaxed nonchalant repetition of a topic is probably a sign that the patient is not relaxed at all or that the topic is being used to camouflage more important issues.

As time goes on, communications increase and your "understanding" of the patient enlarges; that is, a subjective point is reached where the conflictual situation and its dynamics make sense *TO YOU*. This is "understanding" and its attainment in no way ensures its reliability. Acquisition is easiest when you endorse a theory of human behaviour which is largely inferential. It is in this soil that the seeds of overinterpretation, over-explanation and excessive attempts to have the patient assume your notions or values grow and flourish. It is crucial that you avoid these pitfalls for, during the course of the sort of psychotherapy that I am attempting to describe, one is very fortunate if one gets two ideas across to the patient which he assimilates and accepts and which are appropriate to his problems.

IMPROVEMENT.

At some time, the patient will begin to improve and this will occur without any interpretations or with very few indeed; if the patient is apparently wholly recovered he will really be at a loss to explain why he got better and how psychotherapy helped him. From this phenomenon, it is not very far to the concept that the content of psychotherapy is much less important than the feeling or relationship. All that might be evident to either party is that the patient delineated his problems more clearly, proposed an action and subsequently was able to carry it through to solution; this process being possible *only* with the support of the physician. Around such events highly speculative concepts such as "transference neurosis", "unresolved transference", the interpre-

SOME PRINCIPLES OF OFFICE PSYCHOTHERAPY

pharmacologic treatment should be based on its efficacy and the patient's attitude toward it; not your feelings about its rightness or wrongness morally.

Anxiety is described as an overwhelming dread of impending dissolution striking at the very core of the person's existence when he feels he will either scream, run, die, have a fit or go insane. These outcomes are all vague and as soon as they become specific the technical word, anxiety, becomes replaced by the technical word, fear. Excessive anxiety grossly impairs communication and it is good practice to sedate or tranquilize him to a point of diminution where communication can be established. To erase anxiety pharmacologically is to do away with the motivation for change so essential to psychotherapy and, in the two, three or four weeks that you are treating the patient pharmacologically, you should trace the source of anxiety. On a superficial level, this is usually a conflict between the demands that the person feels placed upon him by others or by himself and the degree to which he does not meet these demands in his behaviour. The older the person, the greater the anxiety will be. Chronic excessive anxiety should be approached with some caution in office psychotherapy for it is very hard to deal with.

ALCOHOLIC FACTORS.

If a patient comes to your office routinely somewhat inebriated, his communication and his inter-personal contact with you are grossly impaired. This impairment is not improved by dwelling overmuch on the question of alcohol and it is usually refreshing for the patient to have his alcohol intake ignored and a beginning made at his life's dilemmas. If he is unable to begin talk of these and lives solely for alcohol, he must be treated as an alcoholic and this is best done not in individual psychotherapy but in a group situation by people experienced in alcoholism. It is not necessary to dismiss the slightly inebriated patient from your office or adopt a disapproving or an approving attitude towards it. It should be seen as one of the transporting vehicles that got him into your office and though it impairs the interview he is at least there and trying.

SOCIAL FACTORS

Although the patient represents only one of a social matrix where more than one member is ill, you can still effectively alter his understanding, conflictual behaviour and symptoms without seeing the other members. Usually the patient is unaware of this social matrix and, after you are through with his expressed problems, your

focus must switch to his social *milieu* if it is a major contributor to the patient's continuing disability. The classical situation is the unhappy marriage, and here it is in order to insist that your interviews be carried out alternately with the spouse and with your patient. Your role in marriage counselling is to bridge a gulf between the couple by providing a channel through which communication can be maintained until new positions are set up. Generally, by the time marriage has been placed in a doctor's hands, its dissolution has been seriously contemplated and the patient comes to you consciously or unconsciously attempting to make one final try so that he will not feel a failure, without cause, in interpersonal relationships. With marriages, one's goal should be modest and not prejudged as to resolution or dissolution.

GOALS

One of the most important aspects of psychotherapy is to set an appropriate goal for the patient. Goals can only be set from "formulations" and the method at which one arrives at a goal will be demonstrated. If you can improve on one important facet in a patient's life, then his need for psychiatric help from any source will be fulfilled. It often happens that the doctor and the patient enter into a conspiracy where perfection is the goal. This must be avoided. Imperfections will remain and should be changed only insofar as the patient views them; that is, seen formerly as "weakness" they now become "human" in the patient's mind.

CONCLUSION:

It can be said that it is the relationship that counts in psychotherapy and not the information that passes between the two people. The sympathetic, uncritical, accepting, and yet discerning physician can serve as a model for future relationships that the patient should properly develop. Psychotherapy works best on those people who are mildly depressed and anxious with a minimum of referents to the body. Its role in the obsessive, the hysteric and the psychopath is not clear-cut. Despite this, some doctrinaire schools insist that the hysteric is the best prospect for psychotherapy. The role of psychotherapy for the psychotic is debatable. It would seem that some people can do this sort of relating and others cannot; those who can, do so at the expense of not relating to the anxious and depressed neurotic. There are other forms of psychotherapy not mentioned which work as well, if not better, in some groups of patients: for instance, the alcoholic does better in group psychotherapy and the schizophrenic in *milieu* therapy, but these are somewhat institutional and seldom a matter of "office psychotherapy."

ANSWERS TO "ON INSPECTION"

FIGURE 1 — TRICHINOSIS.

An infection by the nematode, *Trichinella spiralis* characterized clinically by

- (1) symptoms due to development of the adults in the intestinal mucosa, i.e. diarrhea usually within 24 hours of ingestion of uncooked pork. (50% of cases)
- (2) symptoms due to migration of the larvae with invasion of skeletal muscle. These are fever, edema of eyelids with conjunctivitis and hennosis, muscular pain and tenderness, maculopapular rash and subungual splinter hemorrhages in the skin, and focal lesions in lungs and brain, etc.
- (3) laboratory findings: eosinophilia of 15-50%; Bachman's skin test with 1:10,000 trichinella antigen positive by the third week of infection.

Diagnosis consists of finding larvae in one of

- (1) deltoid muscle biopsy (see Fig. 10)
- (2) peripheral blood
- (3) cerebrospinal fluid.

Commoner causes of splinter hemorrhages are

- (1) subacute bacterial endocarditis
- (2) scurvy
- (3) trichinosis
- (4) hemorrhagic diatheses

FIGURE 2. — MYXEDEMA

Cardiac complications of myxedema present as one or more of

- (1) angina pectoris subsequent to coronary arteriosclerosis which in turn is favored by hypercholesterolemia.
- (2) pericardial effusion which develops slowly, and rarely, if ever, causes tamponade.
- (3) lowered voltage of all waves on the E.C.G.
- (4) actual heart failure due to myxedema alone occurs very rarely.

Remember that thyroid must be administered slowly in the initial treatment. Too rapid elevation of the metabolic rate may predispose the patient to angina or psychic disturbances consequent to the coronary or cerebral arteriosclerosis which are common in this condition.

FIGURE 3. — CANCER OF THE TONGUE

DIFFERENTIAL DIAGNOSIS:

- (1) benign ulcer — due to jagged teeth, ill-fitting dentures or trauma. Treatment is by bland mouth washes and

removal of the cause. If no regression in two weeks, do biopsy.

(2) syphilis

- (a) primary chancre with lymph node involvement.
- (b) secondary patches: communicable.
- (c) tertiary: gumma or glossitis.

(3) T.B.; a necrotic base with sloping edges, diagnosed by biopsy.

(4) actinomycoses; a necrotic ulcer often develops over the primary deep nodule. The cervical nodes are not enlarged.

(5) carcinoma; begins as an innocent looking indurated area or fissure in a patch of leukoplakia, a papilloma, or a small ulcer, most often on the lateral margins or undersurface of the middle one third of the tongue. Later stages are characterized by pain, salivation, cervical metastases, and terminal hemorrhage.

DIAGNOSIS FROM BIOPSY: CANCEROUS ULCERATION OF THE TONGUE.

Cancer of the tongue is the most frequent type of intraoral cancer (25%). On the anterior two thirds, it is predominately a disease of males, whereas cancer of the base affects both sexes equally. Sixty per cent occur on the lateral edge at the middle one third, 30% on the posterior third and 30% on the anterior third or on the dorsum.

TREATMENT

- (1) surgical removal of the lesion and the lymph nodes draining the area.
- (2) radiation therapy: in aged patients and in those with no evidence of cervical lymphatic spread.

FIGURE 4. — LEUKOPLAKIA

Diagnosis is leukoplakia. Yes, there could be malignant change and the ulcerated area shown is most likely malignant. Patients with leukoplakia should be observed frequently so that such changes can be treated at the earliest opportunity.

FIGURE 5. — ACTINOMYCOSIS

Actinomyces bovis causes "lumpy jaw" in cattle. This man could be a farmer. However, the disease is not communicable and the usual infection

ANSWERS TO "ON INSPECTION"

follows about a week after trauma such as tooth extraction or compound fracture of the mandible, for *A. bovis* resides normally in the mouth. Three clinical syndromes may present;

1. Cervicofacial; commonest.

Involves the face, neck, tongue or mandible with multiple, painful, indurated and bluish-red sinuses discharging pus.

2. Pulmonary;

Involves the lower lobes with fever, productive cough and evidence of consolidation (abscess formation). Direct extension through the chest wall or through the diaphragm may occur, the latter producing hepatic or subphrenic abscess.

3. Abdominal;

Involves the ileocecal area, appendix and pelvic organs with abscess and fistula formation. The picture may commonly mimic appendiceal abscess, carcinoma of cecum tuberculous infection or amebiasis.

Diagnosis involves finding the "sulfur granules" with central mycelia and peripheral clubs, in the pus. The organism can be cultured with difficulty. Combined approach of surgical drainage or excision of accessible lesions with the use of penicillin and tetracyclines constitutes the therapy.

FIGURE 6. — MALIGNANT MELANOMA

This highly lethal tumor arises from a simple mole or benign pigmented nevus. All moles which show any of the following changes should be immediately suspected of having undergone malignant transformation, and should be removed.

1. increase in size
2. change in color, especially an increase in pigmentation
3. pain, irritation, itching or discomfort
4. infection or ulceration
5. bleeding or increase in vascularity
6. appearance of satellite pigmented areas adjacent to the original lesion.

FIGURE 7. — LUDWIG'S ANGINA.

This is a spreading cellulitis reaching the submaxillary triangle from the mouth, often from an alveolar abscess. There is a firm and painful swelling in the floor of the mouth, generally with protrusion of the tongue. The inflammation may progress to such an extent as to cause edema of the glottis and death from asphyxia and toxemia.

Identical signs are often seen with the impaction of a salivary calculus in Wharton's duct; thus, it is well worth-while to palpate the floor of the mouth for a calculus in such a case of brawny edema of the neck.

FIGURE 8. — CANCER OF THE LOWER LIP

Found in an elderly gentleman greatly fond of his pipe.

Microscopically, the tumor is a squamous cell carcinoma, the majority being well-differentiated grade 1 or 2 lesions, Metastases occur less frequently than in other forms of oral cancer: of all patients with lip cancer, 40 - 45% show cervical lymph node metastases at some period.

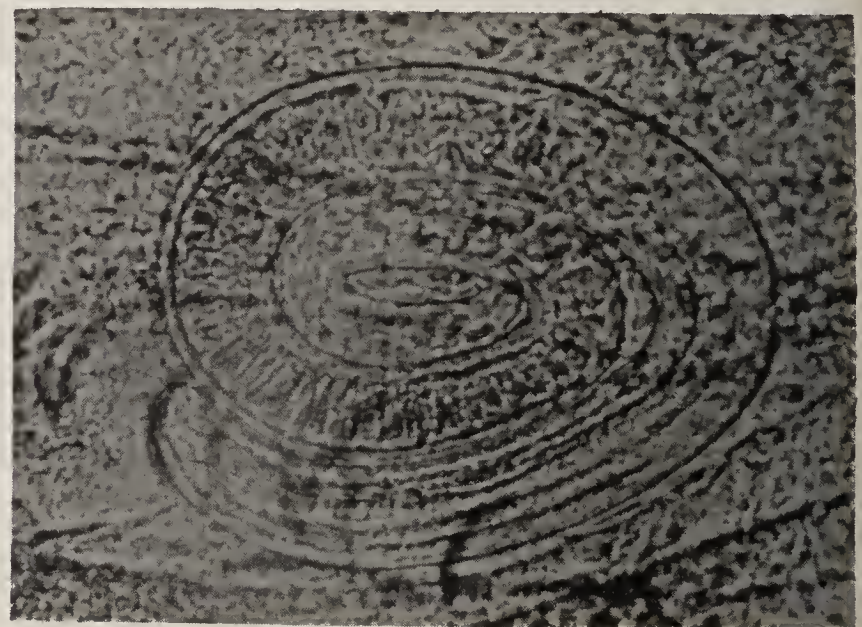
figure 9. — MOLLUSCUM CONTAGIOSUM

This is a mildly contagious, autoinnoculable skin disease caused by a virus of the pox group and occurring more commonly in children. Lesions begin as tiny papules which enlarge over weeks or months to 1 cm. round, pink, waxy, often itchy nodules with an umbilicated crown. They are often multiple and occur especially over the face, trunk, and genitals, excepting the palms and soles of feet.

Histologically, they resemble benign papillomas of the skin except for the umbilication and the presence of round eosinophilic hyaline cytoplasmic molluscum bodies in the prickly cells of the epidermis (the elementary bodies of the virus). Lesions may remain indefinitely without therapy which involves a short trial course of Sulfonamide, Aureomycin or Terramycin if the lesions are multiple. Surgical removal may be required since this management is not always successful. If the lesion is single, however, it must be differentiated from basal cell carcinoma by surgical removal and biopsy.

FIGURE 10

Trichinella spiralis larvae in deltoid muscle biopsy.



ACKNOWLEDGMENT

The authors express their thanks to Dr. C.R. Burton and Dr. J.A. Palmer of the Toronto General Hospital, for the use of their pictures and suggestions.

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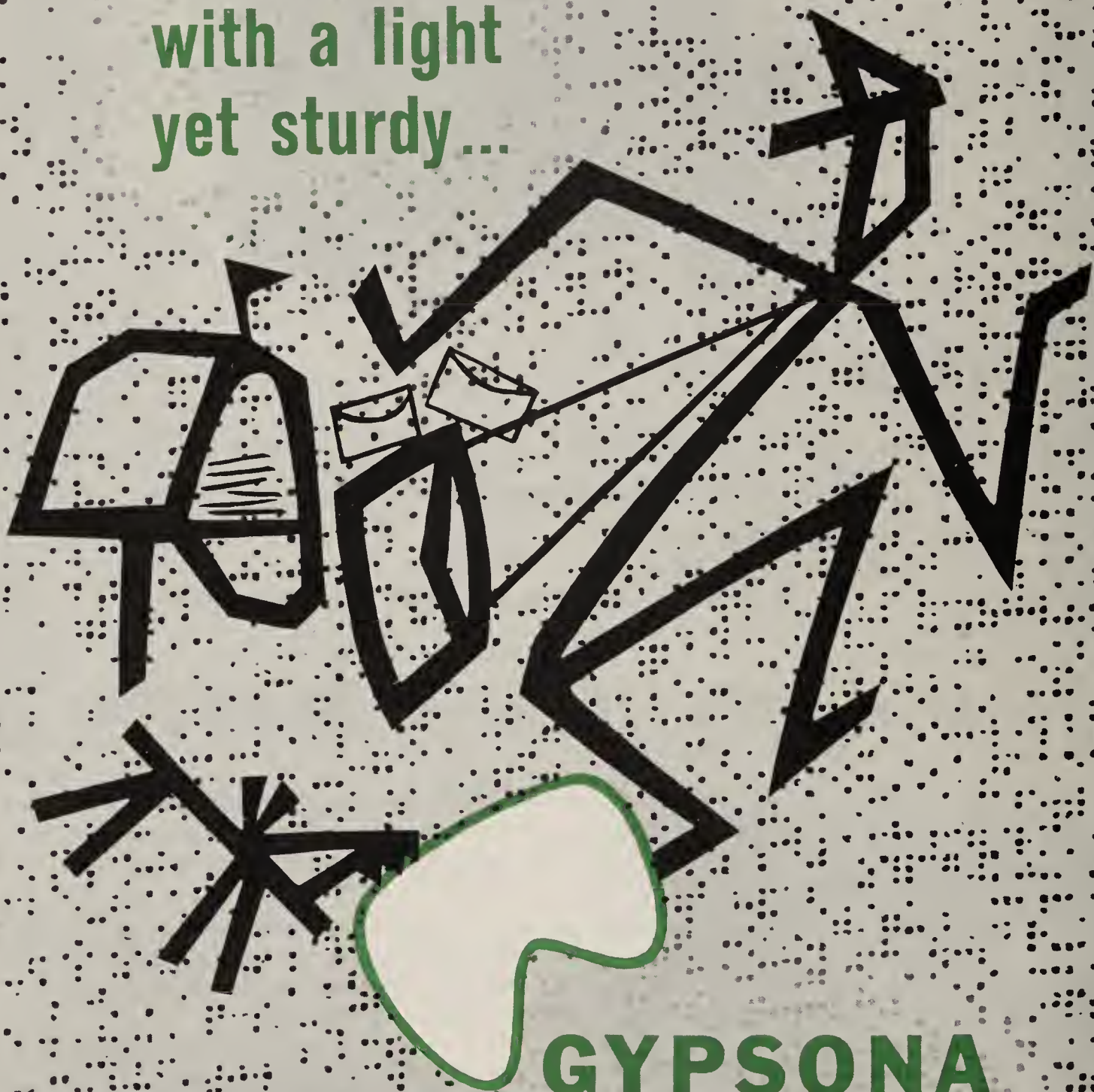
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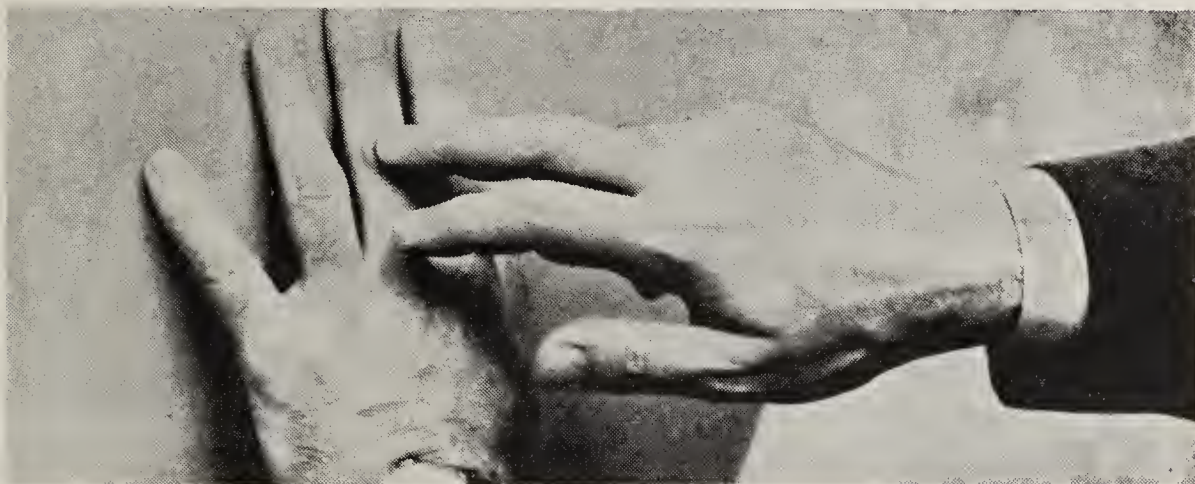


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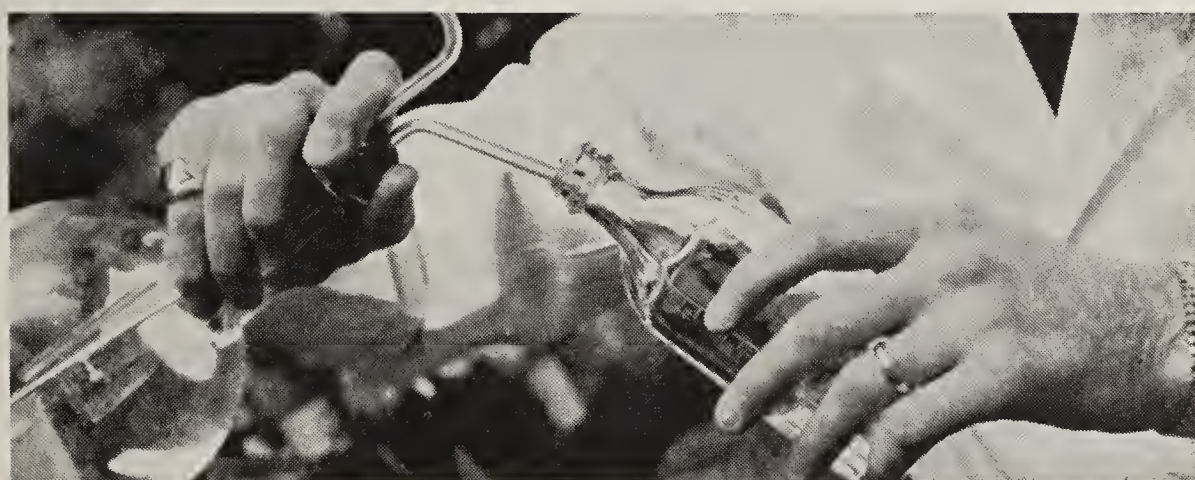


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